Universitat de Girona
Facultat de Medicina

THE USE OF SILVER-COATED ENDOPROSTHESIS IN THE TREATMENT OF PERIPROSTHETIC JOINT INFECTIONS

FINAL DEGREE PROJECT

AUTOR: Laura Dans Vilán
TUTORS: Dr. Antoni Castro Guardiola, Rafael Ramos Blanes

DEPARTMENT OF INTERNAL MEDICINE
Hospital Universitario Josep Trueta
Girona, February 2017

Doy las gracias a todas las personas que me han apoyado y ayudado a lo largo de la realización de este trabajo, sin ellas esta tarea hubiese sido mucho más complicada. Al personal de Stanmore Implants® por ser tan solícitos y ofrecerme ayuda e información, y en especial, agradezco la oportunidad que me ha brindado el Dr. Castro y el equipo de medicina interna, por acogerme en su departamento y enseñarme tanto.

INDEX

1. ABREVIATIONS

AAOS: Americal Academy of Orthopaedic Surgeons

AB: Antibiotic

AP: Pathological Anatomy

BMI: Body Mass Index

CEIC: Comité de Ética e Investigación Clínica

CRP: C Reactive Protein

DAIR: Debridement with Antibiotics, Irrigation and Retention

DNA: Desoxiribonucleic Acid

ESR: Erytrocyte Sedimentation Rate

HIV: Human Immunodeficiency Virus

HJT: Hospital Josep Trueta

MRSA: Methicillin Resistant Staphylococcus Aureus

PIOC: Positive Intraoperatory Cultures

PJI: Periprosthetic Joint Infection

PMMA: Polymethylmetacrylate

PMN: Polymorphonuclear Neutrophil

SAT: suppressive antibiotic Therapy

SPSS: Statistical Package for Social Sciences

USA/ US: United States of America

WMA: World Medical Association

2. ABSTRACT

Background

Periprosthetic joint infection is the most feared complication of joint arthroplasty. The incidence vary between studies and countries being about a 2% and reaching a 5% in revision arthroplasties, but this numbers are expected to rise due to the growing number of arthroplasties that are being performed. The prognosis and evolution of those following revision arthroplasties, who became infected, is worse, than in those in which infection occurs in the first arthroplasty. Periprosthetic joint infection causes pain, discomfort and disability of the joint, and its management implies prolonged and sometimes complex therapies and long hospital stays, that not always succeed in solve the problem, or they do, by leaving the patient with low performance status and reduced life quality. As the current treatments, still doesn't have the best rate of success. The use of silver-coated prosthesis is proposed as a promising treatment, regarding the anti-infective properties of silver and the encouraging results obtained in previous studies.

Purpose

The main purpose of this study is to prove the increment in the treatment success of periprosthetic joint infection by performing an attempted eradication with implant replacement and antibiotics implanting a silver-coated prosthesis.

Design

A randomized, controlled multicentric clinical trial will be performed in charge of the department of internal medicine from Hospital Josep Trueta of Girona, with the participation of hospitals Vall d 'Hebron and Clinic from Barcelona.

Participants

Patients with hip or knee periprosthetic joint infection with surgical indication for attempting implant replacement in 1-stage or 2-satage exchange. Coming to the hospitals Josep Trueta from Girona, Vall d'hebron and Clinic from Barcelona.

3. INTRODUCTION

3.1 ARTHROPLASTY AND JOINT REPLACEMENT

Introduction and definition

An arthroplasty consists in replacing, remodelling or realigning, surgically, by osteotomy or other procedure a damaged or arthritic joint. In case of replacement, an orthopaedic joint prosthesis will be implanted, an artificial ceramic, plastic or metallic implant, which is designed to resemble as much as possible as a normal healthy joint. This is known as replacement arthroplasty. (1)(2)

Epidemiology

In 2010 more than 1 million total joint arthroplasties were performed in USA(3) In Spain about 30.000 per year(4). Incidence vary between countries of study as many factors are involved, like the socioeconomic factors, healthcare system quality or the prevalence of osteoarthritis, the most common cause of joint arthroplasty. But what is clear is that the rate of arthroplasties has increased in the past 2 decades and that it is expected to continue increasing(5). Knee and hip arthroplasties are the most common places of joint replacement. But it can be also performed in many other joints, including ankle, wrist, shoulder and elbow (6)

Indications

The decision whether or not to perform a replacement arthroplasty depends on the functionality and pain caused by the damaged joint, the expected quality of the reconstruction and its durability versus other alternatives; such as, resection arthroplasty, interposition arthroplasty or surgical abstention. Absolut contraindications would be: active infections, not functional limb, and the presence of systemic or chronic diseases that contraindicates the surgery. (2)

Classification

There are many ways to classify the different prosthesis, depending on its structure, characteristics etc.

- **Total / Partial prosthesis:** When the rest of stabilising elements of the joint are entire, it can be replaced only one part of the joint. In the knee, for example, it can be replaced only one compartment of the joint, femoro-patellar, femoro-tibial lateral or medial. That is called an unicompartmental prosthesis. It can also be performed a replacement of the two compartments. This will be a bicompartmental prosthesis, and if the replacement is of the whole joint, then, we will be talking about a total arthroplasty.

- **surface prosthesis:** when a part of the joint is removed, leaving the majority of the structure of the limb entire, we are talking about surface prosthesis. This usually implies high biomechanical preservation of the joint. This are used, for example, in capital femoral or humeral prosthesis.

- **Massive prosthesis (salvage limb arthroplasties):** when it's performed a replacement of the whole limb joint, sometimes including part of the diaphysis.

- **Primary or revision prosthesis:** When is the first arthroplasty performed or when the prosthesis has to be removed and replaced. The principal causes, are: wear of the components, stiffness, instability and infection. In frequency order.

- **Constricted prosthesis**: we are talking about constricted prosthesis when some of the normal movements of the joint are restricted. The degree of constriction is variable, going since the whole display of movements until just movement of flex- extension with or without rotational movement associated.(1,2)

- **Implant characteristics**

  - **Materials**: An arthroplasty can be composed by one only piece, or by several made of the same or different materials. Polyethylene and metal, for example, can give structural support, allow direct or indirect fixation and also be part of the friction pair. Metal (usually titanium) against a polyethylene surface is the most common combination of materials. Others include: ceramic-polyethylene, metal-metal or ceramic-ceramic. This materials, allow effective and complex reconstructions, being infection, the most feared complication. Other disadvantages would be the typical ones from this union of the components, such as wear of the implant or fatigue fractures.

  - **Fixation**: The common way of fixation of the prosthetic components to the bone is with cement (polymethylmethacrylate, PMMA) but there are others, such as, biological fixation, which implies an integration of the implant into the bone.(1)(2)

Complications

- **Painful arthroplasty:** There are many causes which can be the reason of pain in the reconstructed joint. It can be due to secondary causes, but in some cases, the source of pain remains unknown. An excessive physical activity or high expectations regarding the arthroplasty, can be an explanation to this complains. Secondary causes can be intrinsic, as for example due to infection, instability, synovitis, bone lysis and loosening of the implant, joint stiffness, lesion of the extender system or entrapment syndromes, but can also be due to an extrinsic reason, such as: heterotopic ossification, complex regional pain syndrome, tendinopathy, periprosthetic fractures, neurologic lesion acute or chronic, peripheral vascular disease or referred pain.

- **Instability:** This can appear as a clear luxation of the joint, or more subtle as periprosthetic pain or sense of instability, which makes it necessary to confirm and study the possible cause. Luxation appears more often in shoulder or hip arthroplasties and can obey to the collision between the components or other structures, when the limits of the movement permitted are overpassed, or when the contact between the materials is lost. On the other hand, knee total arthroplasties, are

more prone to produce subtle symptoms of instability, as a sense of failure of the prosthesis, difficulty in going up or downstairs, and it is more often associated with pain in the periprosthetic structures and joint stiffness. In the case of bad positioning of the components, it can be enough with revision and adequate relocation. If this does not work, or there is dysfunction of the soft parts associated, it may be necessary to introduce a constricted prosthesis or with restricted mobility.

- **Bone lysis and loosening of the implant:** Bone lysis appears due to the activation of osteoclasts in response to the interaction with certain particles and release of cytokines. This mechanism, ends, promoting a loosening of the components and, at the same time, becoming a new source of mobility and increasing bone destruction. It is a chronic complication. Fact that makes a difference between bone lysis and aseptic loosening of the components, which is usually more acute and of early apparition, and is often secondary to an inappropriate surgical procedure. Signals of failure are: mobilization of the implant and collapse. In cemented arthroplasties, moreover, another significant sign, would be the apparition of lineal radiolucency of more than 1 mm surrounding the components. All this radiologic signs should be referred to the areas of De Lee for the cup and Gruen for the femoral component.

  In the cases in which the components are fixed and well positioned it may be enough with polyethylene replacement and substitution of the bone loss with bone graft. If this is not the case, a revision surgery should be performed.

- **Periprosthetic fractures:** This kind of fractures can occur within the surgery and can be detected at that moment, or post-surgically, in the context of a traumatism or due to bone loss caused by failure of the implant.

  In femoral periprosthetic fractures the classification of Vancouver is the most accepted one. (table 1)

  Treatment depends on the stability of the implant. With fixed implant, not displaced fractures can be treated with conservative treatment. Whereas, displaced ones, would need surgery (following the same principles as the rest of fractures from this bone segment). In case of instability, it is necessary a revision of the device, fixating the new

component in healthy bone. If there's bone loss or not very good quality of it, it may be necessary the use of massive prosthesis or bone implants. (1)(2)

Table 1. (7)

Vancouver classification of femoral periprosthetic fractures		
Type	**location**	**Subtype**
A	trochanteric	(G) greater trochanter (L) lesser trochanter
B	Around or just distal to the stem	1. Stable stem 2. loose stem 3. poor bone stock
C	Well below the stem	

3.2 PROSTHETIC JOINT INFECTION

Introduction and definition

Prosthetic joint infection, also known as periprosthetic joint infection, is defined as infection involving the joint prosthesis and adjacent tissue. It is considered one of the main complications and reasons of failure of the joint arthroplasty.

Joint replacement is nowadays a frequently surgical procedure, which is expected to continue to rise. While the majority of the implants successfully provides pain relief and reestablish joint functionality, a minority of cases suffers failure of the prosthesis and will require additional surgery at some point during the life of the device. While few of the endoprosthesis implanted will become infected, appropriate recognition and management is crucial, in order to preserve function and prevent morbidity, as it is still an important burden for the individual patient as for the global health care industry.(6)

Epidemiology

The incidence of periprosthetic joint infection is about 2% in US and remains a major cause of failure of the implant, being the third cause for both, knee and hip arthroplasty failure (after aseptic loosening and instability of the device), and the third cause of prosthetic revision. This fact is important because the consequences and morbimortality are worse than in those who had revisions following aseptic failure. (8)(9)

The true burden in this case, is not the rate of infection in patients undergoing arthroplasty, but the impact of this infections on both, the patient and the healthcare system when they occur. Complications include pain, discomfort, long hospital stays and treatments. At worse, needing further surgery. This all can lead to long term disability or death(6). Moreover, the annually cost of infected revisions to US hospitals was estimated around 500 million $ (by 2012). This numbers are expected to increase exceeding 1.62 billion $ by 2020 in parallel to the number of joint arthroplasties that are being performed, and as a result, so too will the economic burden of this kind of infections(10)

In Spain, it is estimated that in about 30.000 arthroplasties per year that are being currently carried out, the rate of infection is between 3-4%. For primary knee arthroplasty, being about

2,5%, and for primary hip arthroplasty about 1,5%. This data increases in case of revision to a 5,6 and 3,2% respectively. (4). And even more in case of revision due to infection of the device. The rate of relapses and chronic infection is significant. This will be discussed in the treatment section.

Risk factors

There are many different reported factors that can predispose to the apparition of the periprosthetic joint infection, but, not all of them have demonstrated to significantly increase the risk. Regarding this fact, The AAOs guidelines made a review with the most reliable data available.(11)

- Supported by evidence

-Prior infection of the joint (knee)
-Superficial surgical site infection (hip and knee)
-Obesity (hip)
-Extended operative time (>2,5h. hip and knee)
- Immunodeficiency (knee) Including: VIH, diabetes, immunosuppressive therapy, autoimmune diseases (lupus, rheumatoid arthritis, ankylosing spondylitis, Reiter's syndrome…) arthritis, renal disease, liver failure, malnourishment, sickle cell disease, haemophilia, organ transplant.

- Supported by consensus

- Any recent bacteremia or candidemia (<1year)
- Metachronic prosthetic joint infection
- Skin disorders (psoriasis, chronic cellulitis, lymphedema, skin ulcers..)
- I.V drug use
- Recent MRSA colonization or infection (<3years)
- Active infection at other site

- Possible risk factors. Not supported by evidence

- Smoking
- Obesity (knee)
- Use of drains
- Hematoma or use of anticoagulation

Etiopathogenesis

The key factor in the prosthetic joint infection is bacterial adherence on the artificial joint surface. This process is influenced by the prosthetic surface characteristics, presence of dead bone fragments, host factors (immune and non immune), and pathogen factors (number of bacteria, genetic characteristics, virulence…). Once the bacteria has successfully adhered on the artificial joint surface they settle there and display their self-preservation programme (replication, communication, cytokine production, biofilm formation...). This process is perceived by the host immune system triggering the subsequent inflammation response (12)

There are many reported bacteria which can cause prosthesis-related infections. They are summarized in the table below (see Table 2). Between all of them S. aureus and coagulase-negative staphylococci appear to be the most relevant ones, responsible for, at least, half of the infections.(13)

Table 2.

Common causes of prosthetic joint infection

Infection	**% of patients with prosthetic joint infection**			
	Hip and knee		**Hip**	**Knee**
	All time periods	**Early infection**		
Staphylococcus aureus	27	38	13	23
Coagulase-negative *Staphylococcus*	27	22	30	23
Streptococcus species	8	4	6	6
Enterococcus species	3	10	2	2
Aerobic Gram-negative bacilli	9	24	7	5
Anaerobic bacteria	4	3	9	5
Propionibacterium acnes				
Other anaerobes				
Culture negative	14	10	7	11
Polymicrobial	15	31	14	12
Other	3			

(6)

S. Aureus is a virulent microorganism which is typically responsible of infections occurring in the first three months after surgery, whereas the delayed infections (3-24 months) are more often caused by low virulent pathogens, such as, coagulase-negative staphylococci (13). Both, early and delayed infections usually happen as the consequence of perioperative

contamination and are generally associated with local and systemic symptoms, inducing inflammatory response accompanied by the raise of laboratory inflammatory markers. Late infections (>24months), in the other hand, usually occur after a relatively asymptomatic postoperative period, being generally caused by hematogenous seeding, most commonly from soft tissue and skin infections , but also from respiratory, urinary or gastrointestinal tract infections. (12) (14)

There are two ways by which bacteria can adapt to environmental conditions, existing as free planktonic cells or being embedded in what is called biofilm.

This biofilm formation is commonly seen in prosthetic joint infections, and it's a key factor, as it complicates the process and management of the infection. Such biofilms can be formed by both, virulent bacteria as Staphylococcus aureus and by opportunistic pathogens like Staphylococcus epidermidis. When the microbial density is high enough, the volume of released cell-to-cell signaling molecules is sufficient to activate genes involved in biofilm production, a phenomenon called quorum sensing. Bacteria starts to surround itself into a polymeric matrix and grow into organized complex communities with a system of functionality and communication resembling multicellular organisms. It also reduces it's rate of growth, entering into a stationary state. This fact, added to the protective polysaccharide matrix, leads to a resistance to antibiotic effects and protection from the host immune system, creating a barrier, that is not only impervious to antibodies and phagocytes but may also cause phagocytic deactivation. As a result, microorganisms are difficult to eradicate and infection becomes chronic. Furthermore, the biofilm bacterial cells usually elicit less inflammatory response, which also difficulties the diagnosis of this kind of infections. (15–17)

The development of a biofilm on an orthopaedic implant can be described as a cycle of following steps (see figure 1)

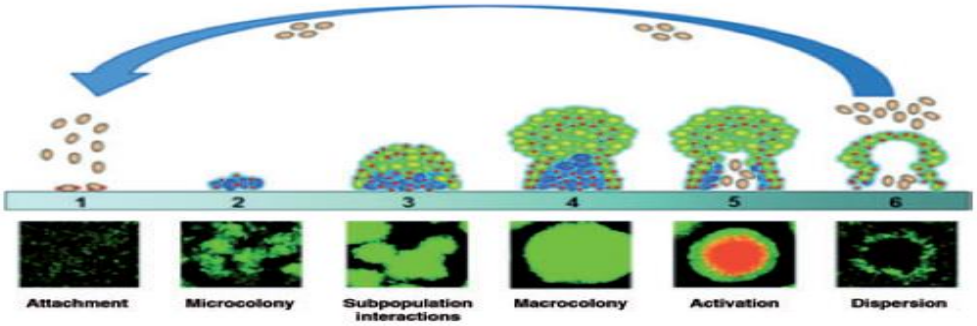


Figure 1.(13)

Classification of PJIs

There are a lot of different classifications in literature. But probably, there are two classic ones, complementary between them, that had demonstrated their clinical usefulness. The first one was proposed by Trampuz and Zimmerli (18). These authors classified PJIs according to the onset of symptoms after implantation into:

- **early infection** (< 3 months postoperatively): This typically occurs as a result of contamination during the surgical procedure, the healing period or from contaminated hematoma. (typically caused by highly virulent microorganisms such as Staphylococcus aureus or Gram-negative bacilli (E.coli…)
- **Delayed infection** (3 months to 2 years postoperatively): In this case the bacteria is usually inoculated during surgery, being typically less virulent microorganisms such as coagulase-negative staphylococci or Priopionibacterium acnes.
- **Late infection** (>2 years postoperatively): This one is consequence of hematogenous dissemination from a bloodstream infection (suspected or proven) typically caused by virulent bacteria, such as S. Aureus, Streptococci and gram-negative bacilli.

Other was proposed by Tsukayama et al (19)

- 1. **Positive intraoperative cultures** (PIOC): occurs when in undergoing revision for a presumed aseptic loosening of the device, two or more cultures result to be positive.
- 2. **Early postoperative infection**: occurring within 1 month postoperatively. The way of infection is the same as in the previous one. Inoculation of the bacteria within surgical procedure.
- 3. **Acute infection (hematogenous)**: when it occurs in a previously well-functioning joint by hematogenous dissemination from another infected focus. There's commonly a recent story of infection (urinary, skin, respiratory…) or invasive procedure performed.
- 4**. Late chronic infection**: Infection that appears insidiously, at least 1 month or until 2 years after surgery. There may be absence of clinical systemic symptoms and only local pain may be present.

Relating these two categories, we can assume that early postoperative infection and hematogenous (Tsukayama et al) and early infection and late infection (Zimmerli et al) can be

considered as **acute infections,** whereas delayed infection (Zimmerli et al) and late chronic are as **chronic infections**.

Diagnosis

There were many different definitions and ways of diagnosing periprosthetic joint infections described along time. But, as there's no gold standard, the most accepted and useful criteria, evidence based ones, are those proposed by the Musculoskeletal infection society (see figure 2)(21)

Definite PJI exists when:

1. There's a sinus tract communicating with the prosthesis OR
2. There are two positive periprosthetic cultures with the same microorganism isolated in two different tissue or fluid samples from the affected prosthetic joint, with bacteria from the normal cutaneous flora (*plasmocoagulase negative staphylococci, Propionibacterium, Corynebacterium, streptococcus viridans*) or just one positive with virulent agents (*S.Aureus, Pseudomonas, Acitenobacter*) or atypical germens (*Lysteria, Pneumococci, Salmonella, candida*) OR

3. Having four of the following minor criteria:

a. Elevated serum C-reactive protein (CRP) >1mg/dl
b. Elevated erythrocyte sedimentation rate (ESR) >30mm^3 1ªh
c. Elevated synovial white blood cell count (WBC) >1700L/mm^3 (>65% PMN for the knee and >3000 WBC/mm^3 for the hip)
d. A single positive culture isolated in tissue or fluid sample with germens from the normal cutaneous flora (*plasmocoagulase negative estaphylococci, Propionibacterium, Corynebacterium,Streptococcus viridans)*
e. Positive histological analysis of periprosthetic tissue (presence of more than five neutrophils per high power field observed in 5 power fields at 400 times magnification)
f. Presence of purulence in the affected joint

** PJI can still be met if less than four of the criteria are present. In certain low-grade infections (such as p. acnes) some of these criteria may not routinely be found even if PJI is present (20)*

Figure 2. Musculoskeletal infection society Criteria (21) Actualized with HJT protocol(22)

Regarding this classification in diagnosing PJI the approach should include (8):

1. A detailed history, physical examination and risk factor identification
1. Joint radiographs
2. CRP and ESR serology
3. joint aspiration and cultures

Detailed history, physical examination and risk factor identification

As the first step in every clinical process, we should explore the onset of symptoms and their evolution as they can vary in order to the timing of apparition and the pathogen involved, as it was highlightened in the PJI classifications explained before.

- **Acute infections**: cardinal signs of infection are usually present (oedema, erythema, tenderness, warmth and with or without fever) there may be cellulitis, hematoma and necrosis of tissue. Acute onset of symptoms and pain. If it was a late onset there may be story of previous infection or trauma and a well- functioning prosthesis until then.
- **Chronic infections:** insidious onset of symptoms with pain and/ or stiffness. Cardinal signs of infection are often absent, being sometimes difficult to differentiate it from an aseptic failure of the device.

It is also important to look for possible risk factors of PJI, the ones mentioned in risk factors section. (8)

Joint radiographs

Due to it ease and rapid use, low cost and ability to rule out other causes, plain radiographs are still the imaging study of choice regardless of their low sensitivity and specificity (23)

- Common findings are:

- Focal osteolysis. Indicated by a band of radiolucency at the interface metal-bone or cement-bone. (24)
- Loosening of components. Which usually occurs rapidly
- Cement fractures
- Subperiosteal reaction.(25)

CRP and ESR serology

The current recommendations are to combine the two blood samples of CRP and ESR in every painful joint arthroplasty, in order to increment the sensitivity and specificity. They are good predictors for both, the absence and presence of infection. When there are normal parameters of both of them we can assume with high reliability that infection is absent (26)

Joint aspiration and cultures

The next recommended step would be WBC count, leucocyte esterase, PMN % and culture samples of the synovial liquid(27)

When WBC count and PMN% are high (>4200/ml and >65% respectively) we can assume that infection is present with high sensitivity and specificity (28)(29). Leucocyte esterase (enzyme released by neutrophils in the context of an infection) has also demonstrated to be an accurate test for PJI, with strong correlation with the other infection markers. In addition is inexpensive, easy of use and rapid (30)

Joint cultures should be performed with three different samples and sent for aerobic/anaerobic cultures, being synovial fluid cultures from blood vial samples preferred to intraoperative swab or tissue sample cultures. (31)

Parvici et al proposed an algorithm in order to make an organised approach in the diagnosis of the periprosthetic joint infection. (ANNEX 1)(8)

Treatment

The treatment of periprosthetic joint infections implies certain complexity, as the main goal is not only to solve the infection problem, but also, to alleviate pain and restore the joint's function. These three goals should be considered in combination, as sometimes the achievement of one of them can be in detriment of another.

The decision of which kind of treatment, medical or surgical should be performed in a given patient, would be made, taking into account: the features of the prosthesis, life expectancy of the patient, desires and expectations, his or her baseline condition and previous functional performance, and also the surgical risk involved.

Regarding the prosthesis, knowing the timings of infection is crucial, as the bacterial status and biofilm formation and maturity would be different and so too will the complexity of it's management. The two time points used are: the time when the prosthesis is placed and the time from then when the symptoms appear. (PJI classifications explained before would be useful at that point). Other aspects to take in consideration must be, the kind of microorganisms involved, as well as their susceptibility to antibiotics, the anatomical location of the prosthesis, and also, the condition of the surrounding soft tissue and the periprosthetic bone.

The current procedures of treatment of PJI are:

- Attempted eradication with implant retention and antibiotics (DAIR)
- Attempted eradication with implant removal and antibiotics
  - With prosthesis replacement (in a 1-step or a 2-step exchange procedure).
  - Without prosthesis replacement (arthrodesis or resection arthroplasty).
- Implant retention and long-term suppressive antibiotics (SAT), without attempted eradication. (32)

<u>Attempted eradication with implant retention and antibiotics (DAIR)</u>

DAIR consists in the retention of the prosthesis attempted by performing an exhaustive surgical debridement of the affected tissue and prolonged antimicrobial therapy, active against biofilm formation. The recommendations are rifampicin, for staphylococcal infections, or fluoroquinolones, for GNB infections (32). The rate of success is estimated in about a 52% (33)
This strategy is recommended in the following cases:

- Having an early post-surgical (<3 months after surgery) or hematogenous infection, with stable implant and skin and periprosthetic soft tissues in good condition.
- Having a short duration of symptoms (≤3 weeks)

❖ *Patients who do not meet the full criteria, may still benefit from this strategy, but each case should be considered individually, since there's no enough evidence and the risk of failure is higher.*

Attempted eradication with implant removal and antibiotics. With prosthesis replacement.

The removal of the implant allows a better control of the infection, and the elimination of foreign bodies and necrotic tissue improves antibiotic activity. However, this procedure also implies a second surgery over this structures that may deplete bone stock and cause dysfunction of the joint. The removal of the device should be considered as a therapeutic option in the following cases:

- Chronic infections
- Loosening of the implant
- Damage of skin and periprosthetic soft tissues
- Absence of antibiotic with good anti biofilm- embedded bacteria activity

Regarding the different procedures, the **2-step exchange** procedure, is the classic treatment of choice. First, the prosthesis and all the foreign material implanted are removed and an exhaustive debridement of the non-viable material, including a synovectomy, is performed. Then, the surgical site is irrigated and a cement spacer with local action antibiotic is placed. After that, systemic antibiotics are prescribed (generally intravenous antibiotic during about six weeks, but is still in discussion). Once the antibiotic therapy is finished and there's no evidence of infection, the prosthesis is reimplanted (2-step) (32). The rate of success with this treatment is estimated in about a 80% (34) But is variable between series. The recommendations for this kind of procedure are:

- As the first choice for chronic PJI
- In the case of failure or candidates not suitable for DAIR

The performance of a **1-step exchange** has emerged in recent years as an attractive possibility, half way between The DAIR and the 2-step exchange. In this procedure, the new prosthesis is implanted in the same surgical procedure as the removal (32). The success rate with this procedure is estimated in about a 77% (35) But is variable between series. It may be considered as a therapeutic option in the following cases:

- In non- immunosuppressed patients, when the bone stock is preserved, periprosthetic soft tissue is in good conditions and the microorganisms involved in the infection (biofilm –embedded bacteria) are susceptible to the antibiotic prescribed.

- In patients with acute infection, when the replacement is not very complex and the microorganisms involved in the infection (biofilm –embedded bacteria) are susceptible to the antibiotic prescribed.(32)

There have been described some specific risk factors for treatment failure with this procedures, apart from the ones previously mentioned (see risk factor section), such as the presence of a sinus tract at the moment of the surgery or the presence of rheumatoid arthritis (6)

Attempted eradication with implant removal and antibiotics. Without prosthesis replacement.

This option may be considered in patients in which the reimplantation is not possible due to the damage of the joint, his or her baseline condition or functional status. The cases must be considered separately, to decide if the most suitable option is an arthrodesis arthroplasty, a placement of a permanent cement spacer (in high complex surgical scenarios, or patients with low functional status or short life expectancy) or a resection arthroplasty (32). The long term success with this strategy is unknown (6)

Implant retention and long-term suppressive antibiotics (SAT), without attempted eradication.

SAT is an alternative strategy that doesn't pretend to eradicate the infection, but to alleviate symptoms or slow them down and prevent the progression of the infection by the indefinite administration of antibiotics. Is the alternative for those cases in which surgical or other medical procedures can not be performed or are expected to be insufficient to eradicate the infection.

Can be recommended in these patients, once the following conditions are met:

- Identification of the causative microorganism.
- Availability of oral non-toxic antibiotics in long term prescription.
- Possibility of close follow- up of the patient
- Absence of pain, loosening or instability of the implant. This factors won't be reverted by SAT.

The patients with indication of SAT must be carefully selected. The temptation to use this strategy, avoiding the performance of complex but potentially eradicative surgery should be resisted. (32)

See ANEX 2 for the use of antibiotics in the different approaches

3.3 SILVER COATED ENDOPROSTHESIS

Due to the raising number of arthroplasties that are being performed, and the importance within its complications, of the periprosthetic joint infection, many research has focused on the development of anti-bacterial coating surfaces.(36).

Current knowledge and applications of silver

Taking into account the pathogenesis and mechanism of adhesion of bacteria to metallic surfaces, Silver has appeared as a promising material to achieve this purpose. Silver is a well-known agent for its anti-infective properties. The uses of this metal, goes back to the past millennia. Ancients, used silver for many medical conditions, mostly for empirical use when, bacteria as the source of infection, was still unknown. Silver was used in many configurations, such as container for liquid, coins, foils, solutions or colloids. Over time, the uses of silver, were extended to wound dressings, dental hygiene or aye conditions and as an agent for the treatment of burns and ulcers, it was widely used until 1940s, when penicillin was discovered. (37)

Nowadays, due to the growing importance of preventing bacterial adhesion to the biomedical devices. Silver has emerged up, and is being extensively investigated and currently used in some medical fields, such as: vascular surgery (vascular grafts coated with silver-antibiotics, central venous catheters…), urology (silver-coated bladder catheters) or orthopedics (silver-coated fixation pins) (38).

Antibacterial properties

The anti- infective mechanism of silver, is based on its property of disruption of the bacterial membrane, The Ag+ ions binds to bacterial DNA and to the thiol groups of different proteins and enzymes, inactivating both, bacterial replication and the metabolic process, resulting in disruption of the membrane and death of the bacteria(39).

It was demonstrated that silver coated substrates prevent the adhesion and growth of bacteria, having biocidal effect in S. Aureus, S. epidermidis and E. coli and even MRSA in vitro (39). Also, studies in vivo were performed in animal model with significantly reduction of the infection rate (40). Recently, with the promising results of this previous studies, some

companies have started to incorporate the silver into the surface of the orthopaedical implants. The studies accomplished in order to prove the efficacy of this new developed devices, where made in high risk population of infection, such as oncological patients who required limb salvage surgery and the implant of what is called megaprosthesis. This studies, one cohort study and one clinical trial, reported that the rate of early periprosthetic infection was significantly diminished by the addition of silver to the surface of the device, and recommend the use of this kind of prosthesis not only in revision cases, but also, as the primary implant in oncological limb salvage arthroplasties (in hip arthroplasties). This studies also suggested that silver coated implants may also improve the management and resolution of infection if it occurs. The results, that this studies provided, proved to achieve a higher rate of success in the treatment of reinfection with DAIR in the silver coated group comparing with the non-coated one, affording further complicated and prolonged treatments.(41)(42)(43)

Side effects of silver

One important concern about the utility of silver was the possible secondary or toxic effects due to the local and systemic release of the ion. Silver toxicity has been reported to appear at serum levels as low as 0.3 mg/mL with clinical manifestations such as argyria, leukopenia, or alterations in renal, hepatic, and neural tissues. Therefore, at the time of incorporating silver onto the prosthetic surface, is convenient to take this issue into account, in order to reach the adequate concentration to reduce the bacterial adherence to the device, but not high enough to provoke systemic toxicity (38). However, some studies In vivo with silver-coated prosthesis implantation have been carried out in animal model (40) proving the absence of toxic side effects. Lately, another trial in human model (44) was also performed, in which no signs of local inflammation were seen, neither corrosion of the implant, metallosis or argyria. However, studies were mean term and more data about long term utility of the silver- coated prosthesis is needed in order to elucidate this issue.

4. JUSTIFICATION

There are many different reasons that motivates and emphasise the importance to accomplish this study.

In first place, it is important to remind that, even though, the incidence of prosthetic failure due to infection, is not very high (around a 2%) it is still being a feared complication. It implies long hospital stays, pain, discomfort, and additional medical or surgical treatments, that not always, succeed in resolve the problem.(6) As it was previously explained, prosthetic joint infections are often difficult to cure, as the bacteria are deeply adhered to the prosthetic surface and are able to resist against the action of the host immune system and antibiotics. The result, in many cases, is a revision arthroplasty. with the risks implied in the surgery itself, added to the higher rate of prosthetic reinfection and worse evolution seen in the revision implants. This all, ends, in many cases, leaving the patient with chronic infection, disability, dysfunction of the joint and, at last, reduced life quality. (6)

Another important burden, is seen from the point of view of the sanitary healthcare system. Nowadays, the number of arthroplasties being performed is increasing, mostly, due to the ageing of the population, and, as a result, so too will the possible complications involving the procedure, meaning an important hospital expense owing to the fact that prolonged stays are required, different medical and surgical procedures may be performed and not to mention the additional cost in case of further revision arthroplasties. In US the annually cost in 2012 was estimated in about 500 million $ and this numbers are expected to increase, exceeding 1.62 billion $ by 2020.(10)

Recently, many studies have been focused in the development of new materials for the prevention of the bacterial adherence and biofilm formation, in order to prevent infection and to improve it's management. Silver has proved to be an agent with anti-infective properties, used in many other medical fields (38). The studies carried out to investigate it's utility proved the efficacy of the silver ions in reducing the rate of infection in vitro and in vivo, without any toxicity or local or systemic secondary effects, and even suggested the improvement in the following management if reinfection occurs(45)(43). The clinical studies in human models were performed in high risk patients, oncological patients, who needed limb salvage surgery. (41)However, due to the encouraging results obtained in those patients, literature suggests, that this kind of prosthesis may be useful for a wider use (46). In that sense, our thinking is

that, we should perform a study in common arthroplasties to prove the efficacy of silver in this field in patients with PJI who need a revision arthroplasty. Due to the fact that, the rate of success with the current treatments is not as high as we would like it to be, added to all the complications in case of failure that we have mentioned, we think that those patients would be the most benefited, with an improvement in health and life quality. Moreover, there's no previous clinical study which proves the efficacy in this kind of patients, and the results, if favourable and cost-effective, would be very interesting and useful in the future approach and management of the periprosthetic joint infections, not only beneficial for the patient, but also for the sanitary healthcare system.

5. HYPOTHESIS:

Treatment of periprosthetic joint infection with attempted eradication with implant replacement and antibiotics, introducing a silver-coated prosthesis will increase the rate of success of the treatment versus the implantation of a classic non-coated prosthesis, in patients with PJI who need revision arthroplasty.

6. OBJECTIVES

6.1 MAIN OBJECTIVE

To assess the efficacy, in the eradication of infection, of silver-coated endoprosthesis, in patients with failure of the device for infective causes, who need revision arthroplasty, versus the implantation of a classic non-coated prosthesis.

6.2 SECONDARY OBJECTIVES

- To assess if there is any difference in the rate of success in the treatment of periprosthetic joint infection, in patients treated with prosthesis replacement and antibiotics, of a silver-coated prosthesis versus the classic non-coated prosthesis. Depending if there is a knee or a hip replacement.

- To assess if there is any difference in the rate of success in the treatment of periprosthetic joint infection, in patients treated with prosthesis replacement and antibiotics, of silver-coated prosthesis versus the classic non-coated prosthesis. Depending if the replacement was performed in a 1-stage exchange or in a 2-stage exchange.

- To assess if there are any cases of toxicity or adverse local or systemic effects caused in patients with PJI treated with prosthesis replacement and antibiotics, with the implantation of a silver-coated prosthesis.

- To appraise if there are any differences between the number of further debridements needed in the patients treated with implant replacement with silver-coated endoprosthesis versus the treated with the non-coated prosthesis.

- To assess if there is a difference in the time it takes the treatment to fail, if failure occurs in the group treated with silver-coated prosthesis, versus the non-coated group.

7. METHODOLOGY

7.1 STUDY DESIGN

In this study a randomized controlled clinical trial will be performed. The study will be multicentric, as we are talking about a not very prevalent pathology and we would need the cooperation of other centers in order to achieve the number of participants necessary for the study. The clinical trial would be performed in Hospital Josep Trueta Hospital of Girona, Hospital Vall d'Hebron and Clinic from Barcelona. The duration of the study would be about 4 years.

- **Randomization methods**

In order to avoid the selection bias, the patients included in the study will be assigned in a group randomly, we will use a computer with the spss software by an external researcher. The investigator will not be aware of which treatment has been assigned to each patient and will not have access to the randomization sequence.

- **Masking techniques**

In order to avoid the detection bias we will perform a simple blind clinical trial. The ideal would be a double blind clinical trial, but as long as the surgeon cannot be a blind investigator, as he or she will see which prosthesis is going to be implanted. The patient will be the one who does not know which treatment was performed. However, the surgeon, will not be aware of what treatment is being given until the new prosthesis is implanted. Acting in this way we can ensure the same conditions for both groups, at least in the first part of the surgery.

7.2 POPULATION OF INTEREST

Our population will be composed by those patients with knee or hip prosthesis that suffer from infection of the device.

- **inclusion criteria:**

  - Patients with 18 years or older
  - Patients who have voluntarily accepted the participation in the study after understanding and signing the informed consent.
  - Patients diagnosed pre-surgically with knee or hip PJI, candidates for attempted eradication with implant removal and antibiotics and prosthesis replacement

- **Exclusion criteria**:

  - Patients with huge damage of the joint, who require large reconstructions or limb salvage surgery.
  - Patients with high surgical risk
  - Pregnancy
  - Patients who need revision arthroplasty due to other reason of failure.

- **Withdrawal criteria:**

  - Patients not willing to comply with the protocol
  - Medical reasons (adverse event) under investigator criteria
  - Signature of the revocation of information consent in order to not to continue the study.

Subjects withdrawn from the trial will not be replaced and will be included in the statistical analysis.

7.3 SAMPLING

The sampling method in this clinical trial will be consecutive. Every patient coming to the hospitals selected for the trial, who fulfill the inclusion and none of the exclusion criteria, will be asked to enroll the clinical trial. Clinicians will explain what is the trial about and what are the two possibilities of treatment, including the advantages, disadvantages and the possible complications for each one. Then, the information sheet (ANNEX 3) will be given to the patient. He or she will be encouraged to read it carefully and to ask for any question or doubt. If the patient understands and accepts the procedure, he or she, should sign the informed consent (ANNEX. 4) and will be, finally, included in the trial.

- **Sample size**

Regarding the results published in previous studies, and also based in the data collected in Hospital Josep Trueta, we have estimated that the rate of success in the treatment of PJI nowadays, in patients treated with attempted eradication with implant replacement and antibiotics (with the implantation of a classic non-coated prosthesis) is about a 65%. Therefore, assuming an alpha risk of 0,05 and a beta risk of 0,2 in a bilateral contrast, we will need 79 patients in each group, to find a statistically significant difference between the two proportions, assuming that we will obtain an increase in the rate of healing, reaching an 85 % of success in the silver-coated group. Increase, that we will consider enough and significant, regarding the results obtained in other previous studies (those made in oncological patients with high risk of infection). We have estimated that the tax of follow up loses will be a 10%, taking in to account the patients that may die, not want to continue the study, or those who will not come to the follow up visits.

Sample size has been calculated using the approach of ARCOSENSO through the “Calculadora de grandaria mostral GRANMO”.

- **Hospital centers selection**

Owing to the fact that we need a big sample size to reach our objectives, we have decided to perform a multicentric study. We will need the cooperation of other centers and we will have

to coordinate all the procedures we are going to perform during the project. This could seem more complicated, but will allow us to obtain and present results in a more reasonable period of time. The coordination of the study will be done in Hospital Josep Trueta (HJT) of Girona. The other Hospitals selected for the trial are, Hospital Vall d'Hebron and Hospital Clinic from Barcelona. This are reference hospitals with wide experience in thisprocedures. Regarding that the cases per year are about 15 in HJT and about 40 in each of the other two, we have estimated that we will need 2 years to recruit the number of patients we need.

7.4 STUDY INTERVENTIONS

In this study we will perform the same surgical procedures, (a 1-stage exchange replacement or a 2-stage exchange replacement, depending on the indication) for the treatment of the PJI in hip or knee, in both groups, being the only difference between them, the kind of prosthesis implanted, a silver- coated or a non-coated one.

- **Materials and services:**

The surgery will take place in the operating room of HJT of Girona, H. Vall d'Hebron, and Clinic of Barcelona, and will be carried out, in charge of the traumatologists experienced in the field from each hospital. Patients will remain hospitalized in the hospital floor of internal medicine or traumatology, until the whole procedure is finished. Traumatologists and internal medicine specialists will be the ones responsible of assessing the evolution of each patient, along with the nurses from each department. The materials needed for the procedure are the ones commonly used in the revision arthroplasties, needing classic non-coated prosthesis for half of the cases and silver-coated ones for the other half. We have decided to use Stanmore Implants® brand, which includes Agluna® technology, a process by which silver ions are "stitched" to the surface of titanium alloy of the implant. We decided that, because it is the brand more experienced in the field, with their products in the current market and being used in the clinical practice. Their technology is backed up by several studies that have demonstrated the efficacy and safety of their products for it's clinical use. Therefore, we will have more confidence and evidence available when comparing our outcomes and drawing conclusions.

- **Procedures**

In order to standardise the procedures we will perform, we will follow the recommendations used in Hospital Trueta protocol.(22)

- **Interventions:**

We will perform an attempted eradication with implant removal and antibiotics with implant replacement in a 2- stage exchange or in a 1-stage exchange, depending on the indication. (see the recommendations in the **PJI treatment section**).

2-stage exchange

In the **first stage**, we will perform a Friedrich of the wound and a wide debridement of all foreign bodies and not viable and necrotic tissue. Then, we will take a sample of the joint's liquid for urgent analysis and culture before opening the capsule. After that, we can perform the capsulectomy and take another 5 culture samples of interfaces and study for intraoperative AP or frozen test. Another debridement and extraction of the foreign bodies, such as the prosthesis components and cement, should be performed. Afterwards we will practice a double setup (withdrawal of all the surgical instruments employed, team change of clothing, new surgical room disinfection, and notching of the new sterile field) before introducing the new cement with antibiotics, (vancomycin 4g and Tobramycin 4g for 40g of cement). Finally, we will close and suture the wound subcutaneously with monofilament. The patient should complete from 6 to 8 weeks of antibiotic therapy, depending on the microorganism isolated (see ANEXO.2) and two more weeks to let the normal skin flora regenerate and to prove the absence of infection. During this days, parameters of infection will be monitored (signs and symptoms, PCR, ESC, WBC, synovial fluid aspiration). If there is evidence of ongoing infection, another debridement may be performed, typically followed by further antibiotic therapy before attempting reimplantation. If infection is absent, next stage can be performed, being the patient hospitalized.

In the **second stage** we will perform antibiotic prophylaxis with cefazolin (60 mins pre-surgery) Surgery should start, again, with Friedrich of the wound, foreign bodies extraction and a

sample for study and culture of the joint liquid. Then, the capsulectomy and pseudomembrane extirpation will be performed, and another 5 interface samples and study for intraoperative AP or frozen test. (If those evidence persistence of the infection, a new debridement and antibiotic therapy should be performed without joint replacement. If after 4 weeks of following, the evolution is favourable, replacement can be retried) After that, debridement and removal of the cement and joint surface rests is necessary to, finally, after performing another double -setup, could implant the new prosthesis. In one group, will be the classic one and in the other, the silver-coated one. Both of them cemented with antibiotic (gentamicin). We will close the wound subcutaneously with monofilament. If the cultures and joint liquid were sterile it will be enough to complete the antibiotic prophylaxis (until 24h after surgery).

1-stage exchange

We will also begin performing a Friedrich of the wound and an exhaustive debridement to ensure a correct cleanness of the tissues. The procedure will be the same explained in the first stage of the 2-stage exchange replacement. Then, we will perform a double-setup and afterwards the implantation of the new cemented prosthesis with antibiotics, silver-coated for one group and classic non-coated for the other. We will close the wound subcutaneously with monofilament. In this case the patient will receive empiric post-surgical antibiotic therapy if the is no identified germen yet with: levofloxacin 500mg/12h+rifampicin 600mg/24h for chronic infections or Cefepime 2g/12h + Daptomicin 10 mg/Kg/d for acute infections, preferably. When culture results are available we will adjust the therapy (see ANEXO.2) Typically 6 weeks of i.v treatment and complete with at least 3 months of oral antibiotic therapy (if the antibiotic is available for oral use) once discharged from hospital.

7.5 VARIABLES

Independent variable

The independent variable of this study is the treatment of periprosthetic joint infection with implant replacement and antibiotics using a silver-coated endoprosthesis as the substitutive implant or a classic non-coated prosthesis. (dicotomic cualitative variable)

Dependent variable

The dependent variable, in this case, would be the success of our treatment. As the absence failure, defined by the presence of: further arthroplasties, prolonged antibiotic therapy suppression, failure of further joint debridements, amputation, arthrodesis or exitus (due to prosthetic infection). When any of this items are present we assume that our treatment has failed. We will assess the success in the following visits every three months recording if any of the mentioned criteria are absent or present by the clinical history, the anamnesis and the physical exploration of the patient.

Secondary variables

- **Appearance of adverse events:** every adverse event described by the patient will be collected in the participant data sheet (ANNEX.5)
- **Number of debridements needed post-surgically:** This information will be collected in the Participant data sheet (ANNEX.5) with a numeric number, during the following period. The final number to include in the statistical analysis will be recorded in the last visit.
- **Time of failure of the device:** This information will be recorded in the participant data sheet (ANNEX.5) as the elapsed time from the endoprosthesis implantation to the apparition of the event of failure. In a numeric number (weeks)

Covariates

We will include as covariates those variables that might be factors of confusion or modifiers of the effect, increasing or minimizing the risk of infection. Including the most relevant risk factors of infection supported by evidence and literature, and those considered risk factors for

the failure of the surgical approach. Covariates will be recorded in the data collection sheet (ANNEX.5) and will be analysed by the clinical history of the patient, anamnesis and physical exploration.

- **Sex** (male /female)
- **Age**
- **PJI location** (knee / hip)
- **kind of surgical procedure** (1-stage / 2-stage exchange replacement)
- **Prior infection of the joint** (presence/absence)
- **Obesity** (>30 BMI) (presence/ absence)
- **Immunosuppression** (including: HIV, diabetes, immunosuppressive therapy, autoimmune diseases (lupus, rheumatoid arthritis, ankylosing spondylitis, Reiter's syndrome…), renal disease, liver failure, malnourishment, sickle cell disease, haemophilia, organ transplant) (presence/ absence)
- **Extended operative time** (>2,5h) (presence/absence)
- **Any recent bacteremia or candidemia** (<1 year) (presence/ absence)
- **Skin disorders** (psoriasis, chronic cellulitis, lymphedema, skin ulcers..) (Presence/ absence)
- **I.V drug use** (presence/ absence)
- **Recent MRSA colonization or infection** (<3years) (presence/ absence)
- **Active infection at other site** (presence/ absence)
- **Previous replacement** (presence/ absence)
- **Presence of a sinus tract** (presence/ absence)
- **Rheumatoid arthritis** (presence/ absence)

7.6 DATA COLLECTION

- **Baseline condition:**

First visit will take place in one of the hospitals selected for the study. The main objective in this first visit is to diagnose the PJI regarding that we have to do that preoperatively to could ask first if the patient is willing to participate in the trial. For that reason, we will follow the musculoskeletal society's criteria mentioned before (see figure2) , excluding the intraoperative criteria (see figure 3). For this purpose, and also to asses if our patient fulfill our inclusion and none of the exclusion criteria, a complete anamnesis and physical

exploration is needed as well as complementary tests, like plain radiograph of the joint, study and culture of the joint's liquid, blood sample with PMN and white blood cell count and PCR and ESR serology have to be performed. It will also be important to collect the general data and medical history of the patient, searching possible risk factors that could be important regarding the results of our study, such as: immunosuppression, history of any previous infection, previous replacement, use of parenteral drugs, skin disorders, presence of rheumatoid arthritis. This are relevant data to take into account into our study for being possible risk factors of infection, and should be recorded. (ANNEX 5)

A nurse will record some basic data of the exploration, such as : vital signs and height and weight, to calculate the BMI (obesity is another risk factor) and a complete exploration of the patient and of the joint should also be performed to assess the external appearance and functionality looking for external infection or if there are any suspicion of another concomitant infection taking place

Diagnostic criteria

1. There's a sinus tract communicating with the prosthesis OR
2. There are two positive periprosthetic cultures with the same microorganism isolated in two different fluid samples from the affected prosthetic joint, with bacteria from the normal cutaneous flora (*plasmocoagulase negative staphylococci, Propionibacterium, Corynebacterium, streptococcus viridans*) or just one positive with virulent agents (*S.Aureus, Pseudomonas, Acitenobacter*) or atypical germens (*Lysteria, Pneumococci, Salmonella, candida*) OR
3. Having four of the following minor criteria:

a. Elevated serum C-reactive protein (CRP) >1mg/dl
b. Elevated erythrocyte sedimentation rate (ESR) >30mm^3 1ªh
c. Elevated synovial white blood cell count (WBC) >1700L/mm^3 (>65% PMN for the knee and >3000 WBC/mm^3 for the hip)
d. A single positive culture isolated in fluid sample with germens from the normal cutaneous flora (*plasmocoagulase negative estaphylococci, Propionibacterium, Corynebacterium,Streptococcus viridans)*
e. Presence of purulence in the affected joint

** PJI can still be met if less than four of the criteria are present. In certain low-grade infections (such as p. acnes) some of these criteria may not routinely be found even if PJI is present (20)*

Figure 3. modification of the Figure 2 criteria for the diagnostic criteria we will follow

- **Study intervention**

The procedure will be performed by surgeons, instrumentalist nurses and anesthesiologist in the operating room. The total procedure time in each stage (from skin incision to closure of the wound) should be registered (a prolonged operative time is another risk factor). As well as complications during the procedure. (ANNEX 5.)

- **Postoperative assessment**

After the procedure, the patient must stay in hospital until the antibiotic prophylaxis is finished, in case of a 2-stage exchange replacement, Or until the hospital antibiotic schedule is finished and the clinician agrees in discharging from hospital to complete with oral antibiotic therapy, in case of a 1-stage exchange replacement. The clinician will check for any complication after the surgery, the nurse will check the vital signs and general status. Inflammatory parameters (PCR, ESC, WBC) will be, also, monitored during the whole hospital stay. All the data will be recorded (ANNEX 5) If everything is fine after that period, the patient can be discharged from hospital.

- **Visits**

The main objective in this study is to assess the rate of success of our treatment defined as the absence of prosthesis failure due to infection. To obtain this information, we will follow the evolution of each patient every three months during one year. In each visit, we will check the absence of: amputation, arthrodesis, antibiotic suppression treatment, further joint replacement or failed debridements due to infection. Items, that, if present, we have described as the failure of our treatment. We will get this information by the study of the patient clinical history, anamnesis and physical exploration, assessing also the absence of external infection signs, that may suggest arising of infection, and CRP monitoring. If our patient was exitus, we will study the case, to asses if it was due a to prosthesis related cause and record the information. We will also record the number of debridements or extra treatment needed. All the information will be collected in the participant data sheet (ANNEX 5) The patient can also make an appointment any time if there is any problem or complain about the device.

7.7 SCHEDULE OF ASSESSMENT

	Pre-surgical time			Hospital time					Post-hospital time			
	-3 d	**-2 d**	**-1 d**	**0**	**6 weeks**	**2 w**	**1d**	**2d**	**3m**	**6m**	**9m**	**12m**
First visit (traumatology floor)												
-PJI diagnosis (anamnesis+ physical exploration+ complementary tests) - check Inclusion/ exclusion criteria -give the information sheet+ informed consent to sign												
Surgical preparation (traumatology floor)												
- anesthetic evaluation -check vital signs -optimize glycemia and nutritional state												
Intervention (1st stage) (operating room)												
- Remove the old prosthesis, cement and not viable tissue -take culture samples -add cement with AB **(2-stage exchange**) or implant the new prosthesis **(1-stage exchange**) -register time and complications												
Postoperative time (traumatology floor)												
-check vital signs and symptoms - evolution (PCR) -Check postsurgical comlications - antibiotic therapy					**2-stage ex** **1-stage exchange** (complete last 3months of AB therapy at home)							
-check vital signs and evolution (aspect of skin and wound, PCR)												
Intervention (2nd stage of 2-stage exchange) (operating room)												
-Remove the cement and not viable tissue -take culture samples -implant the prosthesis A/B -Register time and complications												
Postoperative time of 2-stage exchange (traumatology floor)												
-check vital signs and ev. -finish AB prophylaxis												
Visity (outpatient service)												
- assess the evolution - Record information												

8. STATISTICAL ANALYSIS

- **Descriptive**

Firstly, we will describe the characteristics of our study population recording our cualitative variables in frequency tables for each group of study.

The cuantitative variables, such as the age, or number of further debridements will be presented by the mean with its standard deviation if we can assume a normal distribution or by the median with its confidence interval if the distribution is not normal. Normal distribution will be tested with the Kolmogorov-Smirnov non-parametric test of the equality of continuous, one-dimensional probability distributions.

- **Bivariate**

First, it will be important to assess if the randomization performed has distributed our population homogeneously between the two groups of study, because if not, our results could be affected by this randomization error. In order to appraise that, we would perform a chi-square test to compare the categoric variables, a t-student to compare cuantitative variables with normal distribution or a Mann-Withney test for those cuantitative with not normal distribution. Then, a multivariable analysis adjusted for covariates that resulted significant in this bivariate analysis, that could modify the association between our main variables should be performed.

In order to analyse our primary objective, to know the association between the kind of prosthesis we have implanted and the rate of success of the treatment, we will use the chi square test, regarding that we are working with categoric variables. To analyse for covariates we will use the t-Student or Mann-Whitney test as described previously.

- **Multivariate**

To appraise the contribution of main variable and the covariates that resulted significant in the previous bivariate analysis we will use a logistic regression model. We will assume a confidence interval of 95% and a p value of $< 0,05$ to consider that there is a difference statistically significant.

- **Survival analysis**

To test if there are differences in the time of failure of the two different prostheses studied we will compute Kaplan-Meier survival curves for each group and compare the proportions not failing at any specific time and at the end of study and test if there are significant differences between groups with the logrank test.

- **Stratified analysis**

To assess our secondary objectives, the possible differences in the results, depending on the location of the arthroplasty performed (knee or hip) and also depending on the kind of surgery performed (1-stage exchange or 2-stage exchange), we will make a stratified analysis for this data. We know, for other previous studies, that there are differences regarding the rates of infection, but as there is not previous evidence with the silver-coated prosthesis implantation, it would be important to elucidate this issue, in order to take it into account in further studies.

9. WORK PLAN

- **1ST Stage. Preparation (2 months)**

The principal researchers will be the ones involved in this phase. The objective is to conduct a literature research to prove the importance of the study, to elaborate the research protocol and to present it to the CEIC (Comité de ética e investigación clínica) for evaluation and approval.

- **2nd Stage. Coordination (2 months)**

The principal researchers along with the research collaborators from each center, will be the ones involved in this phase. The objective will be to coordinate and standardize all the procedures involving the trial and data collection. For this purpose we will schedule a first meeting to explain and discuss all the process and following telematic (videoconference) and in-site, meetings to assess the evolution until the end of the trial.

- **3rd Stage. Field research (38 months)**

All the study staff from each center will be involved in this phase. The objective, in this case, is to recruit all the patients needed for the trial, regarding the inclusion and exclusion criteria, to divide them in the two intervention groups randomly, to make the anamnesis and the physical exploration checking possible risk factors, and to perform the treatment approach indicated for each group, assessing the evolution and vital signs. After that, the patient can be discharged from hospital. The follow up will be performed by the principal researchers and equivalent collaborators from the other centers, within the first year after surgery. Patients will be cited every three months to assess the evolution and record the information obtained.

- **4th Stage. Data collection (38 months)**

Principal researchers and equivalent co-operators from the other centers, will be the ones involved in this Phase. The objective will be to collect the data while the trial is being carried out and register it in the database. An external collaborator will review the information obtained regularly, to assess its quality and verify that the protocol is being followed.

- **5th Stage. Data analysis (2 months)**

Principal researchers and collaborators from the other hospitals, along with a statistical consultant will be involved. The objective is to process and analyse all the information obtained using the appropriate statistical tests.

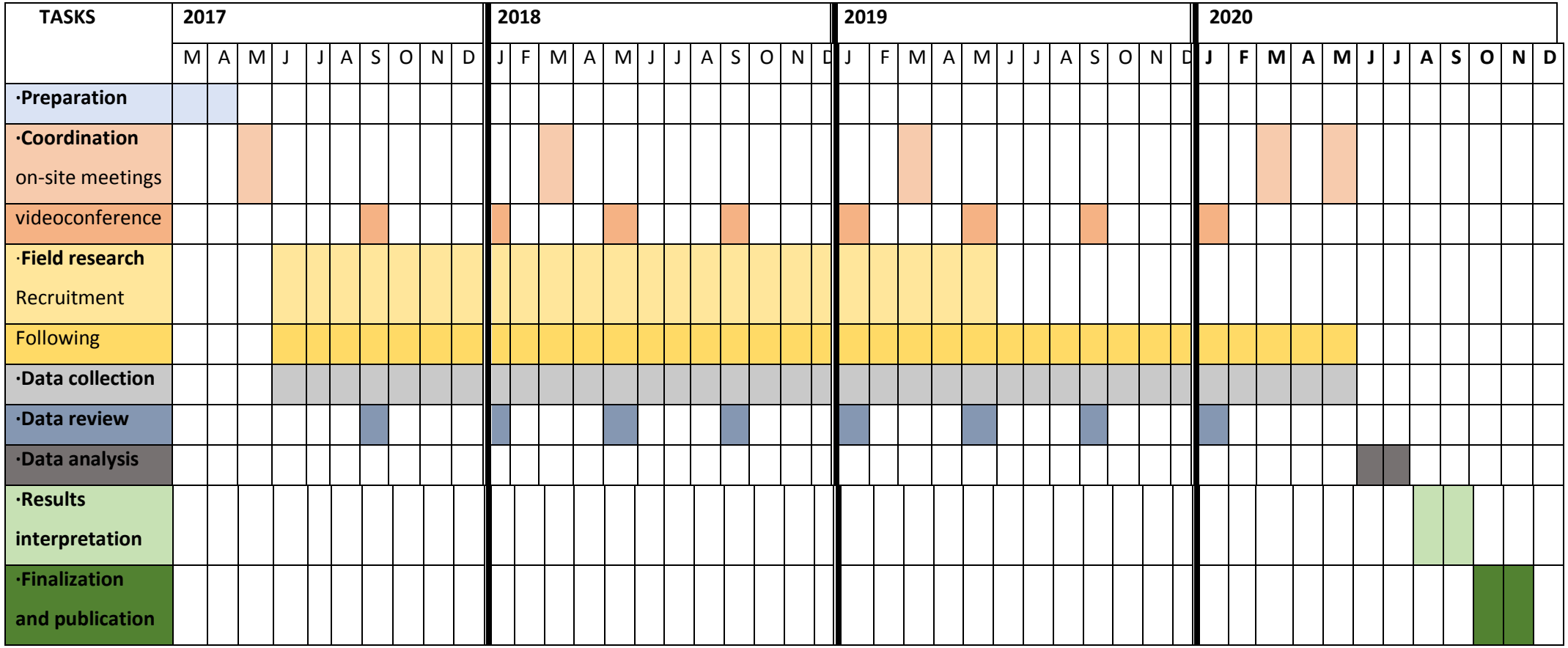
- **6th stage. Results interpretation (2 months)**

The principal researchers will be the ones involved in this phase. The objective will be to interpret and discuss the results obtained, to draw conclusions and analyse the outcome.

- **7th Stage. Finalization and publication of the results (2 months)**

The principal researchers will the only ones involved. We will elaborate the final report with all the conclusions and information drawn and send for publication in different journals.

9.1 CHRONOGRAM



10. ETHICAL AND LEGAL ASPECTS

This clinical trial is subjected to the principles of the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human subjects (1964). As one of the main important things we must take into account in order to perform this study is to respect the ethical principles that characterize a good clinical practice.

Regarding the organic law 15/1999 of the 13th of December about confidentiality and protection of personal data. All the information collected during the study will be kept confidential, and will not be used with other purposes out of the clinical exercise or the research practice. All the data will be treated in an homogeneous and not discriminative way.

Respecting the principle of autonomy, all the participants will be properly informed about all the procedures, interventions and implications of this study. They will receive an information sheet (ANNEX 3) and an informed consent (ANNEX 4) for the inclusion in the study. It is important that the patient reads and understands this information, in order to decide whether or not to join the study in a totally voluntary way. The patient will also be informed that is free of leaving the trial at any point and for any reason, with no consequences in the treat or medical assistance he or she might receive.

This clinical trial will be under the jurisdiction of the spanish law of biomedical investigation *(Real Decreto Legislativo 1/2015, de 24 de julio, por el que se aprueba el texto refundido de la Ley de garantías y uso racional de los medicamentos y productos sanitarios*.) and the Spanish drugs and health products law (*Real Decreto 1090/2015 del 4 de diciembre por el que se regulan los ensayos clínicos con medicamentos, los comités de ética de la investigación con medicamentos y el registro español de estudios clínicos*). The study will be registered in eduraCT and will have to be approved by the Clinical Research Ethics Committee (CEIC) of the Hospitals selected for the trial. Our patients will also be insured for any damage they might suffer during the trial.

This clinical trial will also preserve the principles of non maleficiency and beneficiency. There is not much data available about the results that we will obtain with the treatment under study and our hypothesis is not yet proven, but our thinking, regarding all the previous studies, is that we would reduce the rate of failure comparing with the treatment currently

used, and with no increase in the risks, as they are the same involving the surgery and the device related ones. Previous studies confirmed, also, the absence of toxicity of silver, so we assume that it is a safe and beneficial treatment for our patients. Nevertheless, as there is not much previous experience, we will be in alert for any adverse effect that may appear.

11. STRENGHTS AND LIMITATIONS

In the first place, it is important to assume that our study might have a detection bias. As we have explained in the study design section, we have to perform a simple blind trial, owing to the fact that the surgeon will forcibly know which kind of prosthesis is implanted, with the possibility of this, affecting in the performance of the procedure. The patient will not know which treatment was performed so we will minimize the risk, at least, in this part.

Due to the fact that, the incidence of PJI is not very high, we would need the participation of other hospital centers, in order to achieve the number of participants we need for obtaining significant results in a reasonable period of time. This fact can be challenging at the time of coordinating the study and obtaining comparable results. For that reason, we will standardize the protocol regarding the procedures we are going to perform (following the HJT protocol), and the way the data should be collected. We will schedule an informative and following meetings to assess the progress of the study in the centers selected.

The fact that we need quite a long period of time to achieve the number of participants required, restricts the time for the follow up, as we want to present results in within a reasonably period of time. This goes in detriment of our objectives, whose results will be incomplete, as the rate of delayed and late infection implying failure of the implant can occur until 2 years after the surgery (delayed) or later (late infection). It would have been also interesting to assess the improvement in life quality in those with silver-coated implant. It would be interesting for further investigation.

The main burden we might found, if the results are favourable, is if it would be really applicable in a practical way, regarding the cost-effectiveness of the treatment. Silver-coated prosthesis would be a huge expense for the public sanitary health system. But if the results are as good as they promise, maybe the reduction in the time and number of hospital stays, the further treatments needed (meaning another revision arthroplasty in some cases) and the improvement in the performance and patient's life quality, can pay for itself, as some authors suggested. This subject will be interesting for further investigation.

12. FEASIBILITY

Study staff

In this clinical trial we are going to work with a multidisciplinary team. Patients will be seen and followed by the medical team from the departments of traumatology and internal medicine from the selected hospitals, and along with the nurses in charge of each department will assess the evolution and record the data from each patient. The surgery will be in charge of the traumatologists from each hospital. The team we will work with has a wide experience in this kind of procedures. However, due to the fact that we will collect data from different hospitals, we will have several meetings to standardize the protocol and to assess the progress. Coordination will be conducted by the principal researchers from Hospital Josep Trueta.

We will hire an external statistic in order to get advice with the statistic analysis.

Available resources

We assume that, as the medical and surgical procedures we are going to perform are the same that we will be doing to the patients affected with PJI regardless of their participation on the trial, the materials, staff, surgery rooms and a place in traumatology or internal medicine floor, will be ready and available to receive and treat our patients.
The only difference will be the kind of prosthesis implanted. We will acquire 79 silver - coated prosthesis from Stanmore-implants® to treat half of our patients and 79 classic non-coated prosthesis to treat the other half.

Patients

We assume that, having a number of cases coming to HJT per year about 15 and about 40 in each of the other two hospital centers selected (Hospital Vall d´Hebrón and Hospital Clinic from Barcelona), we will have about 95 patients per year to include in our trial, but we have estimated 2 years for achieving our sample size, regarding those patients that would not want to participate or if the cases are less than expected. However, the recruitment of patients will stop when the sample size is reached, and the follow-up when the last recruited makes a year since the surgery. In that sense, we expect to carry out a clinical trial feasible regarding the time, personnel and material resources.

13. BUDGET

	QUANTITY	COST	SUBTOTAL
SERVICES AND MATERIAL			
Statistical expert for data analysis	**160h**	**35€/h**	**5600€**
Clinical research associate	**40mx4h**	**30€/h**	**4.800€**
Centralized database	**1**	**5.000 €**	**5.000€**
Agluna®-treated prosthesis	**79**	**1.250€**	**98.750€**
Classic non-coated prosthesis	**79**	**1.000€**	**79.000€**
Printing and paper	**4x 158 patients**	**0,4€**	**250€**
Insurance policy	**1**	**25.000€**	**25.000€**
PUBLICATION AND PRESENTATION			
Publish in Joint & Bone journal	**1**	**2.500€**	**2.500€**
Congress attendance	**1**	**800€**	**800€**
		TOTAL AMAUNT:	**211.700€**

Comments

We assume that, as we are performing a routine procedure regarding the surgical and medical services employed, the national health service will provide those; including: the materials necessary for the surgery, surgery rooms and hospital beds occupation as long as required for the treatment, antibiotic therapy, anesthesia, complementary tests necessary for diagnosing and assessing evolution, and the sanitary personnel. The extra materials needed, services and publication and dissemination costs, will be in charge of the study funders.

We realise that carrying out this clinical trial implies an important monetary expense, and we would need public or private financing by a study sponsor to afford it. Possibly, the company of the silver-coated implants itself (Stanmore implants®) would be interested in this clinical trial as if the results are positive their products would be benefited. They also suggested the

possibility of “attaching the silver” with Agluna® technology to the prosthesis that we already use here, this is an interesting possibility that we will consider.

We understand the elevated cost that it would imply for the public sanitary system to use this kind of implants routinely, but if the results are positive, regarding the number of further debridements, further prolonged treatments and extra material and services needed if the treatment fails, along with the gaining in life quality and patient’s performance status it may be cost- effective in long term. This issue will be interesting for further investigation.

14. IMPACT

As it was previously mentioned, periprosthetic joint infection is still a feared complication of joint replacements, because despite the fact that is not the most frequent, it is the most complicated to resolve, which may leave the patient with a decreasing functional ability and poor life quality. If PJI does arise, it means in most cases prolonged hospital stays and prolonged treatments, that not always are effective in resolving the infection or restoring the function of the joint. Current treatments are not as effective as we would like them to be, as there is still an important rate of failure of the therapies and relapse of infection. This fact, regarding that the number of joint arthroplasties being performed is increasing each year, makes it necessary to find better ways or improve the ones in current use for it's management. In that sense, silver coated endoprosthesis seem to be a good option. It was proved in previous studies made in oncological patients the efficacy in resolving and preventing infection, and is now being implemented for the practical use.

If the results of our study results favourable, we can offer the same possibility for a wider number of patients. In our case, patients with PJI, in which reinfection is quite common. We expect to increase the rate of success in the treatment of PJI, meaning a gain in the life quality of our patients, preventing further interventions, chronic or drastic treatments and maintaining a healthy, painless and functional joint. The results will give more information and experience in the use of this kind of prosthesis for future applications and management of PJI. Opening the possibility of considering the arthroplasty with silver-coated endoprosthesis a future approach in the treatment of PJI.

Long term consequences may be seen, also, in a reduction of expenses, in terms of additional treatments and long hospital stays, meaning an improvement, not only in the patient health and life quality, but also, an improvement in the burden that supposes this pathology for the sanitary healthcare system.

15. BIBLIOGRAPHY

1. fernandez herrero M, Santillana ruiz J, Delgado Martinez A. Cirugía ortopédica y traumatología. 3º ed. Panamericana; 2008. 565-576, 667-676 p.
2. Cervero Suárez J, Noriega Fernandez A. Prótesis articulares. Clasificación y complicaciones. In: Manual del residente de COT - Tomo 1 [Internet]. ; Available from: http://booksmedicos.bogspot.com
3. Center for Health Statistics N. Number of all-listed procedures for discharges from short-stay hospitals, by procedure category and age: United States, 2010. 2010;
4. Ariza J, Euba G. Infecciones relacionadas con las prótesis articulares. 2016;26:380–90.
5. Singh JA. Epidemiology of Knee and Hip Arthroplasty: A Systematic Review. Open Orthop J. 2011;5:80–5.
6. Tande AJ, Patel R. Prosthetic joint infection. Clin Microbiol Rev. 2014;27:302–45.
7. Duncan CP, Masri BA. Fractures of the femur after hip replacement. Instr Course Lect. 1995;44:293–304.
8. Parvizi J, Fassihi SC, Enayatollahi MA. Diagnosis of Periprosthetic Joint Infection Following Hip and Knee Arthroplasty. Orthop Clin NA. 2016;47:505–15.
9. Pulido L, Ghanem E, Joshi A, Purtill JJ, Parvizi J. Periprosthetic Joint Infection The Incidence, Timing, and Predisposing Factors. 2008;466:1710-1715
10. Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J, Bozic KJ, et al. Economic burden of periprosthetic joint infection in the United States. J Arthroplasty. 2012 ;27:61–5.e1.
11. American Academy of Orthopaedic Surgeons, Directors J. The Diagnosis of Periprosthetic Joint Infections of the Hip and Knee: Adopted by the American Academy of Orthopaedic Surgeons Board of Directors. 2010;
12. Gallo J, Kolár M, Novotný R, Riháková P, Tichá V. Pathogenesis of prosthesis-related infection. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2003;147:27–35.
13. Song Z, Borgwardt L, Høiby N, Wu H, Sørensen TS, Borgwardt A. Prosthesis infections after orthopedic joint replacement: the possible role of bacterial biofilms. Orthop Rev (Pavia) [Internet]. 2013;5:65–71. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3718238/pdf/or-2013-2-e14.pdf
14. Gbejuade HO, Lovering AM, Webb JC. The role of microbial biofilms in prosthetic joint infections. Acta Orthop [Internet]. 2015;86:147–58. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4404764/pdf/ORT-86-147.pdf
15. Jacqueline C, Caillon J. Impact of bacterial biofilm on the treatment of prosthetic joint infections. J Antimicrob Chemother [Internet]. 2014;69 Suppl 1:i37-40. Available from:

https://academic.oup.com/jac/article-lookup/doi/10.1093/jac/dku254

16. Aparna MS, Yadav S. Biofilms: microbes and disease. Brazilian J Infect Dis [Internet]. 2008;12:526–30. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1413-86702008000600016&lng=en&nrm=iso&tlng=en
17. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-Joint Infections. N Engl J Med. 2004 14;351:1645–54.
18. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-Joint Infections. 2004;1645–54.
19. TSUKAYAMA DT, ESTRADA R, GUSTILO RB. Infection after Total Hip Arthroplasty. A Study of the Treatment of One Hundred and Six Infections*. J Bone Jt Surg. 1996;78.
20. Parvizi J, Adeli B, Zmistowski B, Restrepo C, Greenwald AS. Management of Periprosthetic Joint Infection: The Current Knowledge. J Bone Jt Surg. 2012;94:e104 (1)-e104 (7).
21. Parvizi J, Zmistowski B, Berbari EF, Bauer TW, Springer BD, Della Valle CJ, et al. New Definition for Periprosthetic Joint Infection: From the Workgroup of the Musculoskeletal Infection Society. Clin Orthop Relat Res [Internet]. 2011;469:2992–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21938532
22. Guardiola AC, Luis M, Lechuz V. PROTOCOL DE DIAGNÒSTIC i TRACTAMENT DE LA INFECCIÓ PROTÈTICA ARTICULAR. 2015;
23. Miller TT. Imaging of Hip Arthroplasty. seminars in muskuloskeletal radiology
24. Lima ALL, Oliveira PR, Carvalho VC, Saconi ES, Cabrita HB, Rodrigues MB. Periprosthetic joint infections. Interdiscip Perspect Infect Dis [Internet]. 2013 [cited 2017 Jan 8];2013:542796. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3760112/pdf/IPID2013-542796.pdf
25. Tigges S, Stiles RG, Roberson JR. Appearance of septic hip prostheses on plain radiographs. AJR Am J Roentgenol [Internet]. 1994 Aug [cited 2017 Jan 10];163(2):377–80. Available from: http://www.ajronline.org/doi/pdf/10.2214/ajr.163.2.8037035
26. Greidanus N V., Masri BA, Garbuz DS, Wilson SD, McAlinden MG, Xu M, et al. Use of Erythrocyte Sedimentation Rate and C-Reactive Protein Level to Diagnose Infection Before Revision Total Knee Arthroplasty;A Prospective Evaluation. J Bone Jt Surg. 2007 Jul 1;89(7):1409.
27. Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Diagnosis and management of prosthetic joint infection: Clinical practice guidelines by the infectious diseases Society of America. Clin Infect Dis. 2013;56(1):1–25.
28. Trampuz A, Hanssen AD, Osmon DR, Mandrekar J, Steckelberg JM, Patel R, et al.

Synovial fluid leukocyte count and differential for the diagnosis of prosthetic knee infection. Am J Med. 2004 Oct;117(8):556–62.

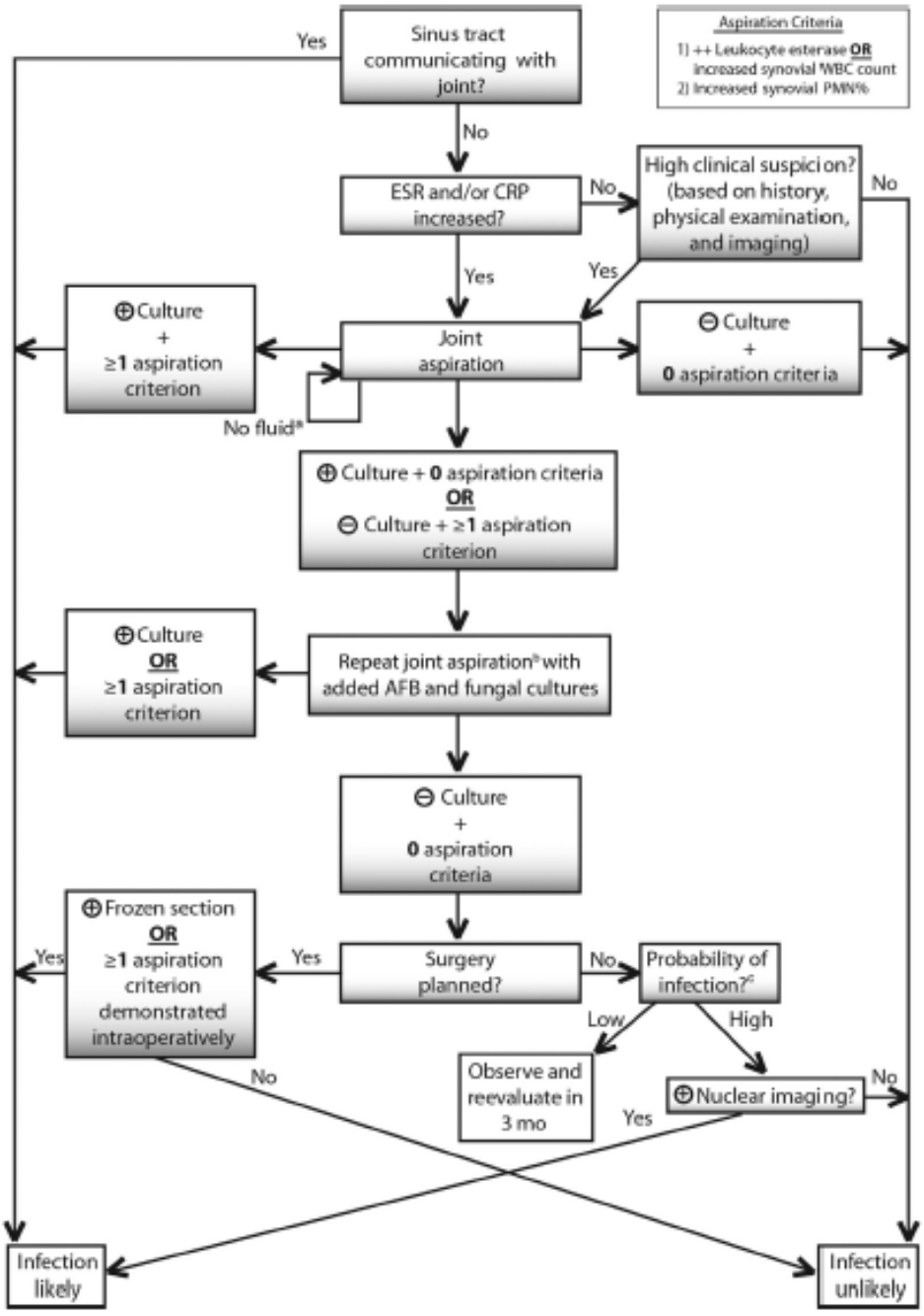
29. Ghanem E, Parvizi J, Burnett RSJ, Sharkey PF, Keshavarzi N, Aggarwal A, et al. Cell Count and Differential of Aspirated Fluid in the Diagnosis of Infection at the Site of Total Knee Arthroplasty. J Bone Jt Surgery-American Vol. 2008 Aug;90(8):1637–43.
30. Parvizi J, Jacovides C, Antoci V, Ghanem E. Diagnosis of Periprosthetic Joint Infection: The Utility of a Simple Yet Unappreciated Enzyme. J Bone Jt Surgery-American Vol. 2011 Dec;93(24):2242–8.
31. Larsen LH, Lange J, Xu Y, Schonheyder HC. Optimizing culture methods for diagnosis of prosthetic joint infections: a summary of modifications and improvements reported since 1995. J Med Microbiol [Internet]. 2012 Mar 1 [cited 2017 Jan 10];61(3):309–16. Available from: http://jmm.microbiologyresearch.org/content/journal/jmm/10.1099/jmm.0.035303-0
32. Ariza J, Cobo J. Clinical practice guidelines for the management of prosthetic joint infections. 2016.
33. Romanò CL, Manzi G, Logoluso N, Romanò D. Value of debridement and irrigation for the treatment of peri-prosthetic infections. A systematic review. Hip Int. 2012;22 Suppl 8(S8):S19-24.
34. Jämsen E, Stogiannidis I, Malmivaara A, Pajamäki J, Puolakka T, Konttinen YT. Outcome of prosthesis exchange for infected knee arthroplasty: the effect of treatment approach. Acta Orthop [Internet]. 2009 Jan 8 [cited 2017 Jan 26];80(1):67–77. Available from: http://www.tandfonline.com/doi/full/10.1080/17453670902805064
35. Buchholz HW, Elson RA, Engelbrecht E, Lodenkamper H, Ro1tger J, Siegel A. MANAGEMENT OF DEEP INFECTION OF TOTAL HIP REPLACEMENT. Jt Bone J [Internet]. [cited 2017 Jan 26]; Available from: http://www.bjj.boneandjoint.org.uk/content/jbjsbr/63-B/3/342.full.pdf
36. Zhang BGX, Myers DE, Wallace GG, Brandt M, Choong PFM. Bioactive coatings for orthopaedic implants-recent trends in development of implant coatings. Int J Mol Sci. 2014;15(7):11878–921.
37. Cao H, Liu X. Silver nanoparticles-modified films versus biomedical device-associated infections. Wiley Interdiscip Rev Nanomedicine Nanobiotechnology. 2010;2(6):670–84.
38. Darouiche RO. Anti-infective efficacy of silver-coated medical prostheses. Clin Infect Dis. 1999 Dec;29(6):1371–7; quiz 1378.
39. Feng QL, Wu J, Chen GQ, Cui FZ, Kim TN, Kim JO. A mechanistic study of the antibacterial effect of silver ions on Escherichia coli and Staphylococcus aureus. J

Biomed Mater Res [Internet]. 2000 Dec 15 [cited 2017 Jan 8];52(4):662–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11033548

40. Gosheger G, Hardes J, Ahrens H, Streitburger A, Buerger H, Erren M, et al. Silver-coated megaendoprostheses in a rabbit model—an analysis of the infection rate and toxicological side effects. Biomaterials. 2004 Nov;25(24):5547–56.
41. Donati F, Di Giacomo G, Ziranu A, Spinelli S, Perisano C, Rosa MA, et al. SILVER COATED PROSTHESIS IN ONCOLOGICAL LIMB SALVAGE SURGERY REDUCE THE INFECTION RATE. J Biol Regul Homeost Agents. 29(4 Suppl):149–55.
42. Hardes J, von Eiff C, Streitbuerger A, Balke M, Budny T, Henrichs MP, et al. Reduction of periprosthetic infection with silver-coated megaprostheses in patients with bone sarcoma. J Surg Oncol [Internet]. 2010 Apr 1 [cited 2016 Nov 28];101(5):389–95. Available from: http://onlinelibrary.wiley.com/doi/10.1002/jso.21498/epdf
43. Seggy Abudu LJHWRGSCRT. retrospective evaluation of the incidence of early periprosthetic infection with silver-treated custom endoprostheses in high risk patients: case control study. isols Conf. 2013;
44. Donati F, Di Giacomo G, D'Adamio S, Ziranu A, Careri S, Rosa M, et al. Silver-Coated Hip Megaprosthesis in Oncological Limb Savage Surgery. Biomed Res Int [Internet]. 2016 [cited 2016 Nov 28];2016:9079041. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5011498/pdf/BMRI2016-9079041.pdf
45. HARDES J, AHRENS H, GEBERT C, STREITBUERGER A, BUERGER H, ERREN M, et al. Lack of toxicological side-effects in silver-coated megaprostheses in humans. Biomaterials. 2007;28(18):2869–75.
46. Grimer R, Parry M, Jeys L. FC-089 Is silver worthwhile on all endoprostheses?

16. ANNEXES

ANNEX1. DIGNOSTIC ALGORITM PROPPOSED BY Parvici et al.



(8)

ANNEX.2 PROPOSED ANTIBIOTIC THERAPIES

Suggested empirical antibiotics for the treatment of PJI in the eradicative attempt of management with implant retention		
Preferred treatment	**Alternative treatment**	**Comments**
Vancomycin or Daptomycin or Cloxacillin iv + Ceftazidime or Cefepime or Meropenem iv	Vancomycin or Daptomycin or Cloxacillin iv + Ceftazidime or Cefepime or Meropenem	Duration until culture results are available

Suggested targeted antibiotics for the treatment of PJI in attempting chronic Oral Antimicrobial Suppression (SAT)		
microorganism	**Preferred treatment**	**Alternative treatment**
Staphylococci (not MARSA)	Cephalexin 500 mg PO or Cefadroxil 500 mg	Dicloxacillin 500 mg or Clindamycin 300 mg PO or Amoxicillin-clavulanate 500 mg PO
Staphylococci (MARSA)	Penicillin V 500 mg PO or Amoxicillin 500 mg PO	Cephalexin 500 mg PO
β-hemolytic streptococci	Penicillin V 500 mg PO or Amoxicillin 500 mg PO	Cephalexin 500 mg PO
Enterococcus spp	Penicillin V 500 mg PO bid to q Or Amoxicillin 500 mg PO	
Pseudomonas aeruginosa	Ciprofloxacin 250–500 mg PO	
Enterobacteriaceae	Cotrimoxazole 1 DS PO	β-lactam oral therapy based on in vitro susceptibilities
Propionibacterium spp	Penicillin V 500 mg PO or Amoxicillin 500 mg PO	Cephalexin 500 mg PO or Minocycline or doxycycline 100 mg PO

(27)

Suggested targeted antibiotics for the treatment of PJI by HJT protocol			
microorganism	Preferred treatment	Alternative treatment	Comments
Staphylococci (not MARSA)	Cloxacilin (2g iv/ 4) + rifampicin (600g iv/ 24h)	Vancomycin (15 mg/kg/12h) or Daptomycin (6 mg/kg /24 h) or Linezolid (600 mg/12 h)	4-6 wk i.v continue with Rifampicin + levofloxacin PO 3 m (750 mg/24h)
Staphylococci (MARSA)	Vancomycin i.V 15 mg/kg q12 h +rifampicin (600g iv/ 24h)	Daptomycin 6 mg/kg/24 h) or Linezolid (600 mg12 h)	4-6 wk i.v continue with Rifampicin+levofloxacin PO 3 m (750 mg/24h)
enterococcus spp	Penicillin G (5.10^6U /6h)	Ampicillin (2g/4h) + amikacin (15mg/kg/24h)	4-6 wk. i.v continue with amoxicillin 1g/8h PO
Pseudomona aeruginosa (or other non-fermenters)	Cefepime 2 g /12 h + aminoglucosid (1d/d)	Ceftazidime 2 g/8h	4-6wk i.v continue with ciprofloxacin (750mg/24h) PO
Enterobacter spp	Cefrtriaxone 2g/24h	Ciprofloxacin 400 mg /12h	4-6wk i.v continue with ciprofloxacin (750mg/d) PO 3m
anaerobic	Clindamycin 600mg/6h		4-6wk iv continue with clindamycin (600mg/6h) PO 3m
candida	Fluconazole (400mg/d)		4-6wk i.v continue with fluconazole (200mg/d) PO 6m
Bacteroids	Metronidazole (500mg/8h)		4-6wk i.v continue 3m PO
Propionibacterium acnes (or other anarerobics GRAM+)	Penicillin G (5.10^6U /6h)	Ceftriaxone 2g/24h	4-6wk i.v continue with amoxicillin 1g/8h PO 3m

(22)

ANNEX 3. INFORMATION SHEET

TITLE: The use of silver-coated endoprosthesis in the treatment of Periprosthetic joint infection

GENERAL INFORMATION

We want to inform you about an investigation research, a clinical trial, that is being carried out in this center and in which you are invited to participate. We would like you to read this paper carefully and to understand why is this research being carried out and what will it imply to participate in it. Then, you can decide whether or not to join the study. We will clarify any questions or doubts you might have.

VOLUNTEER PARTICIPATION

Your participation in this study is totally voluntary. You are free to decide to enter or not as a participant, as well as you are free to withdraw the study any time and for any reason, with any consequences. If you, finally, decide to take part in the trial, we will ask you to sign a consent form. You have been chosen for this study because you have been diagnosed with periprosthetic joint infection and you meet the inclusion criteria and none of the exclusion ones.

It is important for you to know that you can be excluded from the study if the investigator or the sponsor considers it necessary. Reasons should be reasonable and understandable, such as safety reasons or because they feel you are not complying with the procedures established. In any case, you would be properly informed.

DESCRIPTION OF THE STUDY

The main objective of this study is to assess the efficacy in the treatment of periprosthetic joint infections of the silver-coated endoprosthesis versus the classic non-coated one. In order to increase the rate of healing and prevent the relapse and consequences of infection.

In order to achieve this purpose, you will be randomly included in one group. The one which will receive the silver-coated prosthesis, or the one which will receive the classic non-coated prosthesis. The surgical procedures we will perform to you, would be the same that we would perform if you were not participating in the trial. The only difference, will be the kind of prosthesis that we will implant. Depending on your surgical indication, we will try an attempted eradication of the infection with implant replacement in two-stage or one-stage exchange. You will not be aware of which kind of prosthesis you will receive and the selection of the treatment will be completely aleatory. This has to be done in order to not commit bias in our study.

If the surgical procedure consists in a **two-stage exchange** of the implant. First, we will perform the first stage of the procedure, which consists in cleaning, analysing the infected tissue and removing the cement and the old prosthesis. After that, the remaining space will be refilled with new cement with antibiotics. You will have to rest in hospital having antibiotic therapy from 6 to 8 weeks until infection is cured and the antibiotic is completed, and two more weeks, in order to be sure that the tissue has recovered and infection is absent. Afterwards, we will perform the second stage. First, we will give you an antibiotic prophylaxis before going to the surgery room again, to finally, remove the cement with antibiotics and implant the new prosthesis, a classic or a silver- coated one.

If the surgical procedure consists in a **one-stage exchange** of the implant, the procedure will be the same as described in the first stage of the 2-stage exchange replacement, but, in this case, instead of refilling the remaining space with cement, we will implant the new prosthesis in the same surgical act. After that, you will have to remain 6 weeks hospitalized receiving antibiotic therapy, and then, if the evolution is correct, you will complete the three month antibiotic therapy at home.

In case that infection does not resolve. You should stay in hospital in order to perform other procedures or retry the implantation, if possible. On the other hand, if infection is cured, and no other complication after surgery occur, you will be discharged from hospital. We will encourage you to come to hospital again if there’s any complain about the prosthesis, adverse effect or reaction. If you have any doubt or worry, you can also make an appointment for extra visit any time.

The evolution of the treatment will be assessed every three months of a one year following by the doctors in charge of the trial. They will check that the infection is absent, and that you didn't have to perform any other procedures in order to cure the infection, such as prolonged antibiotic therapy suppression, further debridements or further arthroplasties; meaning the failure of our treatment. They will also assess the well-functioning of the device.

BENEFITS AND RISKS

The fact that you are diagnosed with periprosthetic joint infection implies that you have to be treated any way. In the case that you are in the group with the classic prosthesis, you will receive the same treatment as if you do not participate in the study. While, if you are in the silver-coated prosthesis you can benefit from a higher rate of success, less risk of reinfection and a probable better management if it does arise. On the other hand, as our experience with this kind of prosthesis is not very extensive, new complications or adverse events may appear.

Known adverse events involving the arthroplasty, which can affect both groups, can be loosening of the implant, pain, instability, periprosthetic fracture and reinfection. (all of them can lead to a revision and new replacement of the implant or further treatments and procedures).

RESPONSIBILITY AND INSURANCE

You will be insured and you will be compensated for any physical or psychical damage you may suffer during your participation in the study, according to the law.

CONFIDENTIALITY

All the data we will collect about our subjects of study will be registered in a computer database with password protection. The information will be confidential according to the current law (Ley orgánica 15/1999 de proteccion de datos de carácter personal) and your identification will never be disclosed, unless you give permission in order to do so. Only researchers and collaborators will have access to this information, and they will be only allowed to use this data for the research practice.

ECONOMIC COMPENSATION

Your participation in the study would not suppose any additional cost for you and in the same way, you would not receive any monetary compensation.

CONTACT

If there is any doubt or problem during the trial period you can contact with the main researchers

Telf: 972940200

Hospital Josep Trueta. Internal Medicine department

Av/ de França s/n 17007- Girona

Thank you for reading this sheet. If you have any doubt or question about the study, please do not hesitate in asking the researchers or collaborators. In case you decide to participate in the study try to keep this information for your records until the end of the trial. If you are willing to participate, you can continue to read and sign the informed consent.

ANNEX 4. INFORMED CONSENT TO PARTICIPATE IN THE CLINICAL TRIAL

TITLE: The use of silver-coated endoprosthesis in the treatment of PJI with attempted eradication with implant replacement and antibiotics

- I have been properly informed by the investigator about the purpose and implications of the study
- I have read and understood the information sheet
- I had time to think and consider all the information given
- I had the opportunity to ask any question or doubt and be answered
- I understand that my participation is entirely voluntary and that I can withdraw the trial any time, with any consequences for the treat or healthcare I receive
- I have been informed that all my data will be kept confidential, and I give permission to the researchers and collaborators to make use of it in purpose of the study.
- Finally, I agree to participate in this study:

Name of participant _____ NIF _____ Signature	Name of the doctor giving consent _____ NIF _____ Signature

Girona, _____of _____of 20___

ANNEX 5. PARTICIPANT DATA SHEET

GENERAL INFORMATION
Identification code
Name and Surname
Date of birth
Sex
Address
e-mail
Telephone
Day of Hospital admission
Day of discharge from hospital

TYPE OF INTERVENTION	
1-stage replacement	2-stage replacement
PJI LOCATION	
KNEE	HIP

RISK FACTOR COLLECTION		
ITEMS	**YES**	**NO**
Prior infection of the joint		
Obesity (BMI>30)		
Immunosuppression		
Recent bacteraemia or candidemia (<1year)		
Skin disorders (psoriasis, chronic cellulitis, lymphedema, skin ulcers)		
I.V drug use		
Recent MRSA colonization or infection (<3years)		
Active infection at other site		
Previous replacement		
Presence of skin infection or sinus tract		
Rheumatoid arthritis		

PROCEDURES DATA COLLECTION

INTRAOPERATIVE INFORMATION (1st STAGE)	
Total procedure Time (min)	
KIND OF PROSTHESIS IMPLANTED (1-stage exchange replacement)	
Silver-coated prosthesis	Classic non-coated prosthesis
Incidents	

POSTOPERATIVE INFORMATION
Culture sample results
Antibiotic therapy received
Vital signs collected during hospitalization
Days until 2nd stage surgery or until discharge in the 1- exchange replacement
Incidents

INTRAOPERATIVE INFORMATION (2ND STAGE)	
Total procedure time (min)	
Incidents	
Kind of prosthesis implanted	
Classic non-coated prosthesis	Silver-coated prosthesis

POSTOPERATIVE INFORMATION
Culture sample results
Antibiotic therapy
Vital signs collected
Incidents
Days until discharge

FOLLOW-UP DATA COLLECTION

<table>
<tr><th colspan="3">OUTPATIENT SERVICE VISITS</th></tr>
<tr><td rowspan="7">Treatment failure</td><td colspan="2">NO</td></tr>
<tr><td rowspan="6">YES by the presence of</td><td>Amputation</td></tr>
<tr><td>Arthrodesis</td></tr>
<tr><td>Further revision arthroplasty</td></tr>
<tr><td>Prolonged antibiotic suppression therapy</td></tr>
<tr><td>Further failed debridements</td></tr>
<tr><td>Exitus (study cause)</td></tr>
<tr><td colspan="3">Physical examination and evaluation of the joint</td></tr>
<tr><td colspan="3">Number of extra joint debridements needed</td></tr>
<tr><td colspan="3">CRP Monitoring</td></tr>
<tr><td colspan="3">Assess adverse events (Fill in the safety data collection sheet if any complication or adverse reaction is detected)</td></tr>
<tr><td colspan="3">If failure of the device, Time of failure (weeks since the arthroplasty)</td></tr>
</table>

SAFETY DATA COLLECTION SHEET

<table>
<tr><th colspan="3">ADVERSE EVENTS</th></tr>
<tr><td colspan="3">Patient identification code</td></tr>
<tr><td colspan="3">Adverse events observed</td></tr>
<tr><td colspan="3">Start date</td></tr>
<tr><td colspan="3">Finish date</td></tr>
<tr><td colspan="3">Level of severity</td></tr>
<tr><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
<tr><td colspan="2">Severity criteria</td><td>Dead
Vital risk
Hospitalization or extension of hospitalization
Disability (persistent or important)
Important medical event</td></tr>
<tr><td colspan="3">Actions taken to reverse the event</td></tr>
</table>