

# Protocol of a short post-surgical antibiotic therapy in spine infections - prospective, randomized, unblinded, non-inferiority trials(SASI trials)

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## Study protocol

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# Abstract

**Background** There are several open scientific questions regarding the optimal antibiotic treatment of spine infections (SI) with or without an implant. The duration of post-surgical antibiotic therapy is debated. **Methods** We will perform and perform two unblinded randomized -controlled RCTs. We hypothesize that shorter durations of systemic antibiotic therapy after surgery for SI are non-inferior (10% margin, 80% power,  $\alpha$  5%) to existing (long) treatment durations. The RCTs allocate the participants in two arms of 2 x 59 episodes each: 3 vs. 6 weeks of targeted post-surgical systemic antibiotic therapy for implant-free spine infections (two positive microbiological samples); or 6 vs. 12 weeks for implant-related spine infections. This equals a total of 236 adult SI episodes (randomization schemes 1:1) with a minimal follow-up of 12 months. All participants have a concomitant multidisciplinary surgical, re-educational, internist and infectious diseases care. We perform three interim analyses that are evaluated, in a blinded analysis, by an independent Study Data Monitoring Committee. Besides the primary outcome remission, we also assess adverse events of antibiotic therapy, changes of the patient's nutritional status, the influence of immune suppression, total costs, functional scores, and the timely evolution of the (surgical) wounds. We define infection as the presence of local signs of inflammation (pus, wound discharge, calor, rubor) together with microbiological evidence of the same pathogen(s) in at least two intraoperative samples; and remission as absence of clinical, laboratory and/or radiological evidence of (former or new) infection. **Discussion** Provided that there is adequate surgical debridement, both RCTs enable to potentially prescribe less antibiotics during the therapy of SI; with potentially less adverse events and reduced overall costs.

## Introduction

### Background and rationale

Surgical site infections are feared complications of spine surgery of which the volume is expected to increase every year; worldwide [1]. Likewise, community-acquired spine infections (SI) are associated with enhanced morbidity; costs and prolonged hospital stay for the patients [1]. Most scientific papers are rather interested in the epidemiology of SI and risk factors for surgical site infections after spine surgery [2], occurring at 1% to 3% [2-4], rather than the modalities and outcomes of their treatment. Risk factors leading to infection may be multiple. To cite an own example, according to our University Spine Center at the Balgrist University Hospital in Zurich, associated risk factors are a high serum creatinine level, blood loss, or steroid use. Some of these risk factors influence the occurrence of infection only indirectly and act as a confounding element; e.g. fusion surgery, particularly if involving the lumbosacral spine and length of surgery are associated with high blood [2], which itself may become an independent risk factor for infection. This remains the domain of infection control.

In contrast, we are interested if we can streamline the antibiotic therapy after the occurrence of infection; especially by shortening its duration. Such results can be of high value for clinicians. So far, literature on antibiotic regimens in SI is very sparse and strongly evidence-based (instead of basing on evidence).

Most experts recommend a minimum length of (intravenous) antibiotic courses of two to four weeks, often followed by prolonged oral antimicrobial regimens in case of infected osteosynthesis material that was kept in place [1]. Comparative data supporting these individual therapeutic recommendations are lacking. Indeed, one co-author of the current project analyzed the long-term remission with an emphasis on surgical and antibiotic-related parameters. The patients had a median of two surgical debridements with a median duration of antibiotic therapy of eight weeks, of which two weeks parenterally. In 53 cases (80%), the episodes were in complete remission. In cluster-controlled multivariate Cox regression analysis adjusting for the case-mix, the duration of postsurgical antibiotic therapy was completely indecisive regarding the “remission of infection” or “mechanical sequels” [1]. Especially, the following clinically important variables were all unrelated to remission: number of surgical interventions (hazard ratio [HR] 0.9, 95% confidence interval 0.8-1.1); infection due to *Staphylococcus aureus* (HR 0.9; 0.8-1.1), local antibiotic therapy (HR 1.2; 0.6-2.4), and, duration of total (HR 1.0; 0.99-1.01) (or just parenteral) (HR 1.0; 0.99-1.01) antibiotic use [1].

If there is no benefit to long duration antibiotic therapy, it would be important to limit the use of these agents to avoid furthering the problem of antibiotic resistance and adverse events, because the incidence of adverse events related to antibiotic therapy (substantial adverse events in up to 29% of all treatment episodes [5]) and costs genuinely increase with longer duration of antimicrobial administrations [5]. We equally think that, as long as oral antibiotics are used with good bioavailability and bone tissue diffusion, the antimicrobial treatment can be considerably shortened for the benefit of patients and the healthcare sector [6].

## Methods

### Setting

The Balgrist University Hospital (incorporating the University Spine Center Zürich) is a tertiary referral center for SI and affiliated to the University of Zurich, Switzerland. Regarding SIs, it has a multi-disciplinary team composed of five spine surgeons (both Orthopedic- and Neurosurgery), three internist physicians, a hospital pharmacist, specialized wound nurses, musculoskeletal expert radiologists, three specialized nutritionist nurses, two to four dedicated physiotherapists, and up to four Infectious Diseases physicians who are specialized in orthopedic infections. Moreover, this team is supported by a research campus (Balgrist Campus) with BioBanking facilities and a Unit for Clinical and Applied Research with nine study nurses and two personnel with experience in biostatistics and investigational designs ([www.balgrist.ch](http://www.balgrist.ch)). Our study starts at the Balgrist, but is expandable to other national or international centers with experience in the treatment of SIs.

### Study Objectives

We plan a prospective-randomized study of spine infections, for which the intraoperative debridement is part of the therapy. The primary study objective is to evaluate if 6 weeks of systemic and targeted antibiotic therapy postoperatively is not inferior to 12 weeks (non-inferiority trial) in case of infected in

spinal implant-associated infections spine implants left in place. For spine infections without implants, this objective is the evaluation if 3 weeks of antibiotic therapy is not inferior to 6 weeks in postoperative spinal infections without an implant. The switch from intravenous to oral medication will occur early, in absence of sepsis *sensu strictu*, bacteremia or intestinal problems, at latest after one week of treatment. Secondary objectives are the assessments of differences in total costs, sick leave, adverse events, mechanical sequelae, handicap at 6- and 12-months post-treatment and the changes in the nutritional status during therapy. A third objective is the assertion of infected tissue/bone for future studies.

Finally, our study includes BioBanking and the evaluation of the nutritional status of the patient at the beginning and the end of SI treatment. Instead of throwing away, we'll collect intraoperative tissue and/or vertebral bone for ulterior studies. Of note, BioBanking and participation in the clinical trial are exclusive among each other. Patients refusing to provide intraoperative tissue for BioBanking still have the choice to participate in the randomized study and *vice versa*.

### **Definitions and eligibility criteria for participants**

SI is defined as having  $\geq 2$  local manifestations of inflammation (swelling or induration, erythema, local tenderness or pain, local warmth, purulent discharge); together with the same pathogen(s) retrieved in the microbiological culture of at least two intraoperative samples in antibiotic-naive cases. Systemic inflammation (fever, shivering, bacteraemia, hemodynamic alterations) or histological confirmations are facultative. Remission is defined as the absence of any clinical, anamnestic, radiological or laboratory signs of former (or new) SI within 12 months of follow-up. A diagnostic control puncture for the microbiological exclusion of dormant bacteria is not necessary. Of note, internal closed fractures and residual back pain can be interpreted as remission as long they are no signs of infection as defined. Figure 1 resumes the inclusion/exclusion criteria, Figure 2 the study flowchart.

### **Interventions and study conduct**

Upon individual consent of the patient, we will collect clinical, radiological, nutritional and laboratory data from each SI episode. The BioBank will store intraoperative specimens in the Balgrist Campus for 10 years. Table 1 reveals the variables of interest that we collect in the trials. The two RCTs depend on the presence of absence of infected osteosynthesis material:

- *Infected spine material that was not entirely removed (or new material inserted):*

Randomization between 6 and 12 weeks (+/- 4 days) of total antibiotic therapy counted since the first debridement for infection. Early switch to oral targeted therapy.

- *Infected spine without residual material:*

Randomization between 3 and 6 weeks (+/- 4 days) of total antibiotic therapy counted since the first debridement for infection. Early switch to oral targeted therapy.

After randomization, the study participants will be actively followed-up for 12 months. At database closure, we will review the medical charts of all patients to seek for unscheduled visits since the inclusion. This “passive follow-up” can reach up to four years and terminates at the date of database closure. The scheduled study visits take place as follows: visit 1 - Enrollment (Day 1), visit 2 - Day 15 (+/- 5 days), visit 3 - Day 21 (+/- 5 days), visit 4 - Day 42 (+/- 5 days), visit 5 - Day 84 (+/- 5 days). End of treatment visit 6 - Day 21, 42 or Day 84 (+/- 5 days) (only if still receiving treatment after visit 4). Test-of-cure visit - approximately (+/- 60 days) at 12 months (visit 7). The SPIRIT-Figure 3 resumes the timely assessments that are identical for both RCT.

## **Antibiotic agents**

The antibiotic therapy is prescribed by Infectious Diseases physicians with experience in orthopaedic infections, the surgeons in charge of the patient, and/or the internists. It is administered by nurses experienced in orthopaedic infections. Initially, antibiotic therapy is either empiric or targeted to the results of preoperative bone biopsy. After 2-5 days, antibiotic therapy becomes targeted to the pathogens identified in microbiological cultures, and their antibiotic susceptibility profile. The choice of the agent, its intravenous or oral administration route, is usually at the discretion of the Infectious Diseases physician. However, for this study, and in order to achieve a minimal homogeneity, we established a list of “allowed antibiotics” and their recommended doses (Table 2). The investigators must choose among them, unless the causing pathogen of the spine infection is not listed in Table 1 or if an additional surgical site infection (e.g. postoperative pneumonia) needs a broad-spectrum antibiotic treatment. Of note, in this study, we will not test special doses or new indications for antibiotic therapy. Only the duration of the therapy will be determined. All antibiotics are already on the Swiss market and approved by *Swissmedic*, the corresponding authority for medication use. We avoid placebos, topical antibiotics and topical antiseptics; except for the pre-incisional skin preparation and (potential) use. Anaesthesiologists and surgeons are also free to comply with the prevention protocols, even if the patient is already infected, by administering the standard antibiotic prophylaxis (cefuroxime, vancomycin, or clindamycin) for up to three consecutive doses.

## *Pregnancy and breast-feeding*

This cohort, all antibiotics and surgeries, have no specific relations to pregnant or breast-feeding women and their children. Additionally, the study population is likely not to reveal women at procreating age. Thus, pregnant and breast-feeding women are not excluded. The investigators will avoid agents that are not liberated for pregnant or breast-feeding women, according to the Swiss Compendium ([www.compendium.ch](http://www.compendium.ch)).

## **Outcomes of interest**

For the RCTs and BioBanking, we will collect data and biological material. Concerning the randomized trails, Table 1 (bottom) summarizes the outcome parameters. Regarding the investigation of the dynamic changes of the nutritional status during SI care, specialist nutrition nurses will assess the status at

baseline and the end of treatment. In case of severe malnutrition, they are allowed to propose corrective measures already during the SI therapy, because it would be unethical not to intervene only because of study purposes. Finally, the database will be sufficient large to estimate the influence of an underlying chronic immune-suppression (i.e. diabetes mellitus, chronic steroid therapy, dialysis, untreated HIV disease, active cancer in therapeutic or palliative treatment, cirrhosis CHILD C) on SI outcomes and related nutritional status. We also reminder that patients with very severe iatrogenic immune suppression, such as recent solid organ or bone transplantations in the last five years, are exempted from the SASI trials (Figure 1).

## **Allocation and timetable**

After written informed consent will been given to participants (until Day 5 of debridement), the unblinded allocation occurs electronically with a randomization scheme of 1:1 (randomization without blocked or matched variables). The study nurse of the Unit for Clinical and Applied research and/or the co-investigators will implement the allocation sequence into the trial. For both RCTs, we need 36 months of study time; starting in August 2019. Table 3 highlights some key time events.

## **Statistical analyses and sample size**

Both RCT are non-inferiority trials. Remission incidence (at the first attempt of therapy) is set at 5% (5% recurrence in both arms). The clinically maximum acceptable difference (unidirectional non-inferiority margin with binary-outcome categorical variables) is arbitrarily fixed at 10% regarding the primary outcome remission [1]. Assuming a risk of alpha at 0.05 and a power of 80%, it will be necessary to recruit 59 patients in each antibiotic duration arm (short or long). Together with the distinction of the RCT into implant-related and implant-free SI, we would finally need 2 x 2 x 59 episodes, equalling a total of 236 SI episodes within three years. For assessment the formal non-inferiority requirement (regarding the primary outcome "remission"), we will compute with a unidirectional  $p$ -value limit of 0.025. We do not predefine a non-inferiority margin for secondary outcomes such as costs, adverse events, functional outcomes, underlying immune suppression, dynamic changes in the nutrition status and BioBanking.

## *Interim analyses*

When the first 20 episodes of any randomization branch will have a complete follow-up, and again 60 and 120 SI episodes, we perform three interim analyses. On this occasion, we equally check if the expected statistical power for the final analysis will be acceptable. If it is lower than 30%, we will consider the trial will not be able to demonstrate the result, and the recruitment is no more ethical. The most frequent conditional power evaluated under the current trend (i.e. using the information from the collected data) will be assessed [7,8]. The Study Data Monitoring Committee will consist of independent surgeons or physicians, with clinical and statistical experience, not participating in the study. They will decide about the future of the trial, entirely or partially, after each of the three interim analyses. The PI and the Sponsor will present the data in a blinded form to the Data Monitoring Committee. Their members will only know if there is an implant, but ignore allocations to the antibiotic arms.

The intent-to-treat (ITT) population will consist of all randomized patients who signed for the participation. Patients will be analysed according to treatment group assignment regardless of whether the patient receives any treatment or the wrong treatment or is lost to follow-up. The per-protocol (PP) population will consist of all patients who complete the study and who have not deviated significantly from the protocol. The statistical analyses will mostly base on descriptive analyses, group comparisons and a multivariate, unmatched, eventually cluster-controlled, Cox regression analysis adjusting for the large case-mix that we expect. Equally, a Generalized Estimation Equations (GEE) model might adjust for clustering in case of multicentre origin of the patients. The Biostatistician will analyze the datasets in a blinded form (as group A or B), but the PI, the Study Nurses, and the Sponsor will ultimately unblind the allocations for data verification and definition of the ITT and PP populations.

## **Ethical and regulatory aspects**

### *Study registration, ethical conduct and categorization*

The study is approved by the Ethical Committee of Zurich (no. 2019-00646) and registered in the Swiss Federal Complementary Database („Portal“) and in the international trial registry ClinicalTrials.gov (clinicaltrials.gov; no. NCT04048304). This study only makes use of the medicinal products and antibiotic agents that are already authorized in Switzerland. The indication and the dosage are used in accordance with the prescribing information and the international guidelines making this study fall into the category of Clinical Trials A. The study will be carried out in accordance to the protocol and with principles enunciated in the Helsinki Declaration, the Good Clinical Practice guidelines and the Swiss Law. The Ethical Committee receives annual safety reports and is informed about the study stop/end. Substantial amendments are only implemented after a new Ethical Committee approval.

### *Patient Information and Informed Consent*

Participants will be recruited by any of the investigators of the study. Our institution has a standardized procedure for recruiting participants as participant studies are common. Each participant will be informed that the participation in the study is completely voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her medical assistance and treatment in the future. All participants of the study will be provided a Participant Information Sheet and Informed Consent Form entailing sufficient information. For the BioBank, the participants will sign the General Consent for the further use of personal data and biologic material. The investigators affirm and uphold the principle of the participant's right to privacy and that they shall comply with applicable privacy laws and/or the corresponding section of the study specific consent.

## **Safety issues**

### *Monitoring*

The Unit for Clinical and Applied Research of Balgrist University Hospital will assign an independent monitor. Regular monitoring visits at the investigator's site prior to the start and twice during the course of

the study will help to follow up the progress, to assure utmost accuracy of the data and to detect possible errors at an early time point. The monitor will review all or a part of the Case Report Forms (CRF) and written informed consents. The accuracy of the data will be verified by reviewing the above referenced documents. There will be a close-out visit at the study end. During the monitoring, all documents including source data/documents will be accessible for the monitor.

### *Audits and Inspections*

An audit/inspection of this study may be conducted by the competent authority. The quality assurance auditor/inspector could have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study. The investigator will allow the persons being responsible for the audit or the inspection to have access to the source data/ documents and to answer any questions arising. All involved parties will keep the patient data strictly confidential.

### *Early termination of the study (participation)*

The investigators may terminate the study prematurely according to certain circumstances, for example: ethical concerns, insufficient participant recruitment, when the safety of the participants is doubtful or at risk, respectively, alterations in accepted clinical practice that make the continuation of a clinical trial unwise, early evidence of benefit or harm of the experimental intervention. If a patient is withdrawn, the reason will be noted. When possible, evaluations required at the next scheduled visit will be performed at early termination.

### *Treatment by specialists*

All surgeries will be performed in the supervision and participation of an experienced spine surgeon. The antibiotic therapy is ordered and supervised by internists and infectious diseases physicians with therapeutic and academic experience in SI treatments. The current medications of the study patients, as well as possible interactions, will be controlled by the internists several times a week during hospitalization.

### *Definition and assessment of (serious) adverse events and other safety related events*

An Adverse Event (AE) is any untoward medical occurrence in a patient, and which does not necessarily have a causal relationship with the study procedure. A Serious Adverse Event (SAE) is classified as any untoward medical occurrence that: results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity. In addition, important medical events that may not be immediately life-threatening or result in death, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. Participants with ongoing SAEs at study termination will be further followed up until recovery or until stabilization of the disease after termination. The investigators will make a causality assessment of the event to the study. All SAEs must be reported immediately and

within a maximum of 24 hours to the Sponsor-Investigator of the study. SAEs resulting in death are reported to the local Ethics Committee (via local Investigator) within 7 days. Patients with adverse events, and leaving the study, will be treated off-study, without restriction, at the study site.

#### *Case Report Forms, procedure of data analysis and BioBank archiving*

An electronic CRF will be generated for every patient. All relevant study data are recorded by authorized persons in the REDCap<sup>®</sup> electronic data capture tool [9] and archived for a minimum of 10 years. Participating patients will be registered in an enrolment log assigning the participant to his/her study ID. Corrections can only be made by the authorized persons. For data analysis, subject-related data from REDCap will be exported and analyzed in statistics software (IBM - SPSS and/or STATA). Before data export, all patient identifiers will be removed. Patient-source and BioBank data will be registered using subject identifiers. Collection, disclosure, storage of patient-related data is carried out in accordance with Swiss data protection regulations and the Human Research Act. The BioBank will store the intraoperative tissue samples in accordance with their guidelines. Likewise, radiological data are stored in the PACS system according to the standard at the Balgrist University Hospital.

#### *Theoretical risk of the study*

Besides the retrospective identification of patients, we do not see any particular risk for the patients regarding the cohort. For BioBanking specifically; a theoretical additional risk could be the detection of unknown pathologies, if there would be a further work-up of the intraoperative samples. Concerning the RCTs, a theoretical risk could be a higher incidence of recurrences in the corresponding short antibiotic arms.

## **Discussion**

Our cohort with two embedded RCTs seeks to demonstrate a clinically relevant non-inferiority of a shorter systemic antibiotic treatment in adult SI patients; with and without implants [1]; and independently of the surgical drainage technique, the number of debridement, underlying individual chronic immune suppression, the infection localization or the pathogens. Importantly, all study participants have an accompanying multidisciplinary surgical, re-educational, internist and infectious diseases treatment and follow-up. We equally collect intraoperative soft tissues and bone for future (laboratory) studies and assess adverse events, overall costs, functional outcomes and the dynamic changes in the nutritional status of the infected patients; with relation to their therapy and outcome. The studies start in Zurich, but are expendable to other study centers with experience in treating SI.

The primary outcome is “remission at the last follow-up”, but the RCT enable to adjust for different important variables such as the number of surgical debridement, the use of a negative pressure therapy, administration of a parenteral antibiotic regimen or the total duration of antibiotic therapy. As in many field of septic orthopedic surgery, the number of surgical debridement does not formally influence remission rates, which has been shown for chronic osteomyelitis [10], septic native joint arthritis [11],

fracture device infections [12], infected open fractures [11], or prosthetic joint infections [14]. There is very little evidence to guide surgical treatment of patients who require a single versus multiple debridements. Dipaola et al. developed a predictive model for spinal SSIs basing on 128 infected patients. Among thirty clinical variables analyzed, and despite the retrospective nature of their analysis, they have validated four variables being strongly predictive regarding the necessity of multiple debridements: infection due to methicillin-resistant *S. aureus*, bacteremic disease, posterior lumbar spine and use of non-autograft bone grafts [15].

Certainly, the most important variables retrieved from our trials will be antibiotic-related. Most author groups advocate a minimum length of parenteral antibiotic courses of 2-4 weeks and a total duration up to three months [16,17] for SI, although some groups only recommend two weeks of parental therapy [18,19], or even only 2-3 days [20], without further compromising the success. To cite examples, Clark and Shufflebarger treated delayed infections with surgery and 48-72 hours of parenteral antibiotics followed by ten days of targeted oral antibiotics. All infections were eradicated [21]. Likewise, Richards and Emara prescribed systemic antimicrobials only for three weeks, of which 2-5 days parenterally, followed by a 7 to 14 day-course of oral treatment [22].

In the entire field of "orthopedic infections", there are no formal scientific data proving the benefit of a systemic antibiotic therapy beyond six weeks; compared to four to six weeks or even less. Exceptions are by nature expert opinions in previous book chapters or past publications without own database analyses; or the therapy of special microorganisms requiring long-lasting antibiotic therapies such as mycobacteria [23], *Nocardia* spp. [24], actinomyces or fungi [25]. To cite recent and own examples of investigations regarding the overall antibiotic duration, sacral osteomyelitis [26], long bone osteomyelitis [10], fracture-device-related infections [12], spondylodiscitis [26], prosthetic joint infections [14], diabetic foot osteomyelitis [27,28] and many more failed to enhance remission rates, if antibiotics were prolonged beyond four to six weeks; even in presence of an infected implant. Farhad et al. resumed that six weeks of antibiotic therapy was sufficient for all bone-related infections [14]; together with an early switch of oral medication [6]. These emerging and relatively short durations are equally acknowledged by international consensus meetings [30] of surgeons and infectious diseases physicians, who treat these infections and who perform research on them.

There are also studies with less than six weeks of total antimicrobial therapy, especially in the pediatric literature for hematogenous osteomyelitis. In this particular setting, a three-week antibiotic course appears to be sufficient as highlighted by many authors [31-34]. For adults, 38 case series with antibiotic treatment durations of 3 to 4 weeks, including 5 to 36 patients each, revealed cure rates of approximately 80% according to a review published in 2005 [35].

A second issue is the distinction between intravenous and oral antibiotic administration; at least initially. Current textbooks recommend the parenteral route for at least the first two weeks for all osteoarticular infections [1,36-38], but this recommendation is not evidence-based either. There are no predictive clinical markers that would justify prolonged initial intravenous administration. In addition, up to one-third of

patients with chronic bone and implant infections may experience antibiotic-related or catheter-related problems during parenteral treatment [38]. For economic reasons, as well as patient and nurse comfort, parenteral administration should be kept to a minimum [39]. Good bone penetration during parenteral and oral administration has been proven in several reports [40-42] and data suggest that an early switch to oral antibiotics is as effective as prolonged parenteral regimens [43].

A Cochrane review investigated five trials comparing oral vs. parenteral antibiotics in osteomyelitis. There was no statistically significant difference between the two groups in the remission rate twelve months or more after treatment [44]. Glassman et al. successfully treated two patients with SI with oral ciprofloxacin from the start, an antibiotic with excellent oral bioavailability and bone penetration [45]. Even in cases of diabetic foot osteomyelitis, a frequent disease with its hallmark of vascular insufficiency and tissue ischemia, there are no data indicating the superiority of any particular route of delivery of systemic antibiotics [46]. Byren et al. demonstrated that an intravenous course of antibiotics for over four weeks did not enhance cure for the treatment of arthroplasty infections [47]. Zimmerli et al. summarized observational studies that showed the same failure rates of arthroplasty infection treatment despite a prolonged (four to six weeks) period of intravenous treatment [48]. For the treatment of bone infections, there are some antibiotics that have already proven to be effective in oral form. Quinolones, rifampicin, co-trimoxazol, tetracycline or clindamycin have such a good and sufficient oral bio-availability [49].

Our future patient population will comprise all co-morbidities and chronic immune suppressions. For example, we expect 20-25% diabetic patients [50] in our center, along with other immune suppressions such as cancer, advanced cirrhosis and steroid medication. While immune suppression (especially diabetes mellitus) is an acknowledged independent risk associated with healthcare-associated surgical site infections [51], its influence on the remission during a therapy for SI is unknown. Indeed, all current therapeutic concepts for osteoarticular infections in general, do not relay on the presence or absence of immune suppression [1,10,12,26]; suggesting that the surgical debridement and the long antibiotic administration overcome eventual shortcomings of the patients' immunity. Although our SASI trials do not target the association of immune suppression with SI outcomes, we will see if immune suppression tends to decrease remission when we shorten the antibiotic duration.

Finally, our RCT will also give insight in the nutritional status of the infected spine patients. Current literature is departed between experts advocating a causal relationship between malnutrition and occurrence of surgical site infections in orthopedic surgery, while others have retrospectively investigated this relationship and mostly found no associations [52]. Both fractions know even less about the associations and the dynamics of the nutritional status in already infected orthopedic spine patients, and the association of these alterations with remission, functional outcomes and underlying immune suppression; let alone the question of the benefits of nutritional interventions during the combined surgical, physiotherapeutic and antibiotic treatment [53]. This will be *terra nova* that we embed into our trials.

We do not expect major difficulties performing our studies. Despite two prospective-randomized designs (for SI with and without implants) and only 236 different episodes anticipated, the patients' voluntary participation might be low. Likewise, patients who are continued to be treated outside of our center may have been lost to our follow-up or have their treatment changed, because the following physicians do not agree. However, our center is the largest public hospital for surgical SIs in the region, and it is the University Spine Center; so this is unlikely to be a major bias. Lastly and formally, our study participants will benefit from an initializing surgical debridement of infections. Hence, our results will not be valid for the conservative treatment of SI, which must not be confounded with.

## **Declarations**

### ***Ethics approval and consent to participate***

The study protocol was submitted for approval to the Cantonal Ethical Commission of Zurich, Stampfenbachstrasse 121, 8090 Zürich, Switzerland (BASEC 2019-00646). We distributed a written consent form to the participating patients and informed them also orally.

### ***Consent for publication***

Not applicable.

### ***Availability of data and materials***

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### ***Competing interests***

The authors declare that they have no competing interests.

### ***Funding and insurance***

The project starts with an internal grant of Balgrist University Hospital. Additional financing and grants are requested during the project. The Balgrist research insurance is applicable (Insurance police Nr. 14.050.565 Winterthur Insurance). Any damage developed in relation to study participation is covered by this insurance. A copy of the insurance certificate will be placed in the Investigator's Site File and the trial master file.

### ***Authors' contribution***

MB, RS, MF, YA and IU made substantial contributions to the study conception and design.

MB, MF, and IU are engaged in grant searches. IU performs the statistical analyses. All authors participate in the study conduct and the final writing of the manuscript.

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## ***Publication policies***

The sponsor will make every endeavor to publish the data in (a) medical journal(s), to be able to communicate the results to healthcare professionals, the public and other relevant groups. All participants will be sent a free copy of the published article. There will not be any publication restriction and we plan to sort at least three major publications. We will also present preliminary results in national, regional, and international scientific meetings. The main investigators PD Dr. Michael Betz, Prof. Mazda Farshad and PD Dr. Ilker Uçkay will be either first or last authors, in at least two of the three major publications. All investigators indicated in this protocol, and eventually additional colleagues participating in the future, will be co-authors of this study according to their individual contributions.

## ***Trial status***

The study, with the actual protocol version 2, has begun on 5<sup>th</sup> August 2019. The recruitments take place since 1<sup>st</sup> August 2019 and will continue until 2022.

## **References**

1. Billières J, Uçkay I, Faundez A, Douissard J, Kuczma P, Suvà D, et al. Variables associated with remission in spinal SSI. *J Spine Surg.* 2016;2:128-34.
2. Farshad M, Bauer DE, Wechsler C, Gerber C, Aichmair A. Risk factors for perioperative morbidity in spine surgeries of different complexities: a multivariate analysis of 1,009 consecutive patients. *Spine J.* 2018;18:1625-31.
3. Achermann Y, Schroeder G, Tarazona D. Should prophylactic antibiotic prophylaxis be repeated during spine surgery? If so, when? Second International Consensus Meeting on Prosthetic Joint Infection - Philadelphia, USA, July 2018.
4. Shillingford JN, Laratta JL, Reddy H, Ha A, Lehman RA Jr, Lenke LG, et al. Postoperative Surgical Site Infection After Spine Surgery: An Update From the Scoliosis Research Society (SRS) Morbidity and

- Mortality Database. Spine Deform. 2018;6:634-43.
5. Schindler M, Bernard L, Belaieff W, Gamulin A, Racloz G, Emonet S, et al. Epidemiology of adverse events and *Clostridium difficile*-associated diarrhea during long-term antibiotic therapy for osteoarticular infections. J Infect. 2013;67:433-8.
  6. Li HK, Rombach I, Zambellas R, Walker AS, McNally MA, Atkins BL, et al. Oral versus Intravenous Antibiotics for Bone and Joint Infection. N Engl J Med. 2019;380:425-36.
  7. Lachin JM. A review of methods for futility stopping based on conditional power. Statist Med. 2005;24:2747-64.
  8. Snapinn S, Chen MG, Jiang Q, Koutsoukos T. Assessment of futility in clinical trials. Pharmaceutical Statistics. 2006;5:273-81.
  9. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377-81.
  - 10.
  11. Rod-Fleury T, Dunkel N, Assal M, Rohner P, Tahintzi P, Bernard L, et al. Duration of post-surgical antibiotic therapy for adult chronic osteomyelitis: a single-centre experience. Int Orthop. 2011;35:1725-31.
  12. Uçkay I, Tovmirzaeva L, Garbino J, Rohner P, Tahintzi P, Suvà D, et al. Short parenteral antibiotic treatment for adult septic arthritis after successful drainage. Int J Infect Dis. 2013;17:199-205.
  13. Al-Mayahi M, Betz M, Müller DA, Stern R, Tahintzi P, Bernard L, et al. Remission rate of implant-related infections following revision surgery after fractures. Int Orthop. 2013;37:2253-8.
  14. Dunkel N, Pittet D, Tovmirzaeva L, Suvà D, Bernard L, Lew D, et al. Short duration of antibiotic prophylaxis in open fractures does not enhance risk of subsequent infection. Bone Joint J. 2013;95-B:831-7.
  15. Chaussade H, Uçkay I, Vuagnat A, Druon J, Gras G, Rosset P, et al. Antibiotic therapy duration for prosthetic joint infections treated by Debridement and Implant Retention (DAIR): Similar long-term remission for 6 weeks as compared to 12 weeks. Int J Infect Dis. 2017;63:37-42.
  16. Dipaola CP, Saravanja DD, Boriani L, Zhang H, Boyd MC, Kwon BK, et al. Postoperative infection treatment score for the spine (PITSS): construction and validation of a predictive model to define need for single versus multiple irrigation and debridement for spinal surgical site infection. Spine J. 2012;12:218-30.
  17. Zimmerli W. Clinical practice. Vertebral osteomyelitis. N Engl J Med. 2010;362:1022-9.
  18. Bible JE, Biswas D, Devin CJ. Postoperative infections of the spine. Am J Orthop (Belle Mead NJ). 2011;40:264-71.
  19. Lazennec JY, Fourniols E, Lenoir T, Aubry A, Pissonnier ML, Issartel B, et al. Infections in the operated spine: update on risk management and therapeutic strategies. Orthop Traumatol Surg Res. 2011;97:107-16.

20. Kuo CH, Wang ST, Yu WK, Chang MC, Liu CL, Chen TH. Postoperative spinal deep wound infection: a six-year review of 3230 selective procedures. *J Chin Med Assoc.* 2004;67:398-402.
21. Gerometta A, Rodriguez Olaverri JC, Bitan F. Infections in spinal instrumentation. *Int Orthop.* 2012;36:457-64.
22. Clark CE, Shufflebarger HL. Late-developing infection in instrumented idiopathic scoliosis. *Spine (Phila Pa 1976).* 1999;24:1909-12.
23. Richards BR, Emara KM. Delayed infections after posterior TSRH spinal instrumentation for idiopathic scoliosis: revisited. *Spine (Phila Pa 1976)* 2001;26:1990-6.
24. Balagué N, Uçkay I, Vostrel P, Hinrikson H, Van Aaken I, Beaulieu JY. Non-tuberculous mycobacterial infections of the hand. *Chir Main.* 2015;34:18-23.
25. Uçkay I, Bouchuiguir-Wafa K, Ninet B, Emonet S, Assal M, Harbarth S, et al. Posttraumatic ankle arthritis due to a novel *Nocardia* species. *Infection.* 2010;38:407-12.
26. Uçkay I, Jugun K, Gamulin A, Wagener J, Hoffmeyer P, Lew D. Chronic osteomyelitis. *Curr Infect Dis Rep* 2012;14:566-75.
27. Jugun K, Richard JC, Lipsky BA, Kressmann B, Pittet-Cuenod B, Suvà D, et al. Factors Associated With Treatment Failure of Infected Pressure Sores. *Ann Surg.* 2016;264:399-403.
28. Tone A, Nguyen S, Devery F, Topolinski H, Valette M, Cazaubiel M, et al. Six-week versus twelve-week antibiotic therapy for non-surgically treated diabetic foot osteomyelitis: a multicenter open-label controlled randomized study. *Diabetes Care.* 2015;38:302-7.
29. Gariani K, Lebowitz D, von Dach E, Kressmann B, Lipsky BA, Uçkay I. Remission in diabetic foot infections: Duration of antibiotic therapy and other possible associated factors. *Diabetes Obes Metab.* 2019;21:244-51.
30. Farhad R, Roger PM, Albert C, Pelligri C, Touati C, Dellamonica P, et al. Six weeks antibiotic therapy for all bone infections: results of a cohort study. *Eur J Clin Microbiol Infect Dis.* 2010;29:217-22.
31. International Consensus Meeting on Musculoskeletal Infection (ICMMI). Philadelphia, Pennsylvania on July 25-27, 2018. <https://www.ors.org/2018-icm/> (assessed 24 May 2019).
32. Weichert S, Sharland M, Clarke NM, Faust SN. Acute haematogenous osteomyelitis in children: is there any evidence for how long we should treat? *Curr Opin Infect Dis.* 2008;21:258-62.
33. Peltola H, Paakkonen M, Kallio P, Kallio MJ. Prospective, randomized trial of 10 days versus 30 days of antimicrobial treatment, including a short-term course of parenteral therapy, for childhood septic arthritis. *Clin Infect Dis.* 2009;48:1201-10.
34. Vinod MB, Matussek J, Curtis N, Graham HK, Carapetis JR. Duration of antibiotics in children with osteomyelitis and septic arthritis. *J Paediatr Child Health.* 2002;38:363-67.
35. de Graaf H, Sukhtankar P, Arch B, Ahmad N, Lees A, Bennett A, et al. Duration of intravenous antibiotic therapy for children with acute osteomyelitis or septic arthritis: a feasibility study. *J Bone Joint Surg Br* 2004;87:319-20. *Health Technol Assess.* 2017;21:1-164.

36. Lazzarini L, Lipsky BA, Mader JT. Antibiotic treatment of osteomyelitis: what have we learned from 30 years of clinical trials? *Int J Infect Dis*. 2005;9:127-38.
37. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Eng J Med*. 2004;351:1645-54.
38. Trampuz A, Zimmerli W. Antimicrobial agents in orthopaedic surgery: Prophylaxis and treatment. *Drugs*. 2006;66:1089-105.
39. Pulcini C, Couadau T, Bernard E, Lorthat-Jacob A, Bauer T, Cua E, et al. Adverse effects of parenteral antimicrobial therapy for chronic bone infections. *Eur J Clin Microbiol Infect Dis*. 2008;27:1227-32.
40. Mermel LA, Farr BM, Sherertz RJ, Raad II, O'Grady N, Harris JS, et al. Guidelines for the management of intravascular catheter-related infections. *Infect Control Hosp Epidemiol*. 2001;22:222-42.
41. Smilack JD, Flittie WH, Williams TW, Jr. Bone concentrations of antimicrobial agents after parenteral administration. *Antimicrob Agents Chemother*. 1976;9:169-71.
42. Darley ES, MacGowan AP. Antibiotic treatment of gram-positive bone and joint infections. *J Antimicrob Chemther*. 2004;53:928-35.
43. Sattar MA, Barrett SP, Cawley MI. Concentrations of some antibiotics in synovial fluid after oral administration, with special reference to anti-staphylococcal activity. *Ann Rheum Dis*. 1983;42:67-74.
44. Daver NG, Shelburne SA, Atmar RL, Giordano TP, Stager CE, Reitman CA, et al. Oral step-down therapy is comparable to intravenous therapy for *Staphylococcus aureus* osteomyelitis. *J Infect*. 2007;54:539-44.
45. Conterno LO, da Silva Filho CR. Antibiotics for treating chronic osteomyelitis in adults. *Cochrane Database Syst Rev*. 2009:CD004439.
46. Glassman SD, Dimar JR, Puno RM, Johnson JR. Salvage of instrumental lumbar fusions complicated by surgical wound infection. *Spine (Phila Pa 1976)*. 1996;21:2163-9.
47. Berendt AR, Peters EJ, Bakker K, Embil JM, Eneroth M, Hinchliffe RJ, et al. Specific guidelines for treatment of diabetic foot osteomyelitis. *Diabetes Metab Res Rev*. 2008;24:190-91.
48. Byren I, Bejon P, Atkins BL, Angus B, Masters S, McLardy-Smith P, et al. One hundred and twelve infected arthroplasties treated with 'DAIR' (debridement, antibiotics and implant retention): antibiotic duration and outcome. *J Antimicrob Chemother*. 2009;63:1264-71.
49. Zimmerli W, Widmer AF, Blatter M, Frei R, Ochsner PE. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. *JAMA*. 1998;279:1537-41.
50. Toma MB, Smith KM, Martin CA, Rapp RP. Pharmacokinetic considerations in the treatment of methicillin-resistant *Staphylococcus aureus* osteomyelitis. *Orthopedics*. 2006;29:497-501.
51. Al-Mayahi M, Cian A, Kressmann B, de Kalbermatten B, Rohner P, Egloff M, et al. Associations of diabetes mellitus with orthopaedic infections. *Infect Dis (Lond)*. 2016;48:70-3.
52. Uçkay I, Harbarth S, Peter R, Lew D, Hoffmeyer P, Pittet D. Preventing surgical site infections. *Expert Rev Anti Infect Ther*. 2010;8:657-70.
53. Guanziroli N, Hannouche D, Uçkay I. Is malnutrition associated with orthopaedic infections? A single-centre pilot evaluation. *J Hosp Infect*. 2019;101:229-30.

54. Schütz T, Valentini L, Piauth M. Screening auf Mangelernährung nach den ESPEN-Leitlinien 2002. *Aktuel Ernaehr Med.* 2005;30;99-103.

## Tables

Due to technical limitations, Table 1 is only available as a download in the supplemental files section.

**Table 2 - List of allowed antibiotic treatments (empirical or targeted)**

<b>Antibiotic Agent</b>	<b>Allowed Dosing Regimens</b>	<b>Allowed Total Daily Dose*</b>
Levofloxacin PO	500 mg q.12h	750 to 1000 mg
Ciprofloxacin PO	500 mg q.12h	750 to 1500 mg
Amoxicillin/clavulanate PO	500/125 mg q.12h. or q.8h	1000/250 mg to 1500/375 mg
Amoxicillin/clavulanate IV	1000/200 mg q.12h or q.8h	2000/400 mg to 3000/600 mg
Cefuroxim IV	1500 mg q.8h	4500 mg
Ceftriaxon IV	2000 mg q.24 h	2000 mg
Co-trimoxazol PO	960 mg q.12h or q.8h	1920 mg to 2880 mg
Clindamycin PO	300 mg or 450 mg q.6h	1200 mg to 1800 mg
Doxycyclin PO	100 mg q.12h	200 mg
Linezolid PO	600 mg q.12h	1200 mg
Linezolid IV	600 mg q.12h	1200 mg
Metronidazol PO	500 mg q.8h or 500 mg q.6h	1200 mg to 2000 mg
Metronidazol IV	500 mg q.8h or q.6h	1500 mg to 2000 mg
Vancomycin IV	15 mg/kg q.12h	Target serum levels, 10-20 mg/L
Meropenem IV	1 g or 2 g q.12h or q.8h	2 g to 6 g
Piperacillin/tazobactam IV	4000/500 mg q.8h	1200/1500 mg (12 g/1.5 g)

PO = oral therapy; IV = Intravenous therapy: \* to be adapted to renal insufficiency

**Table 3 - Time table of the study**

Activity	2019				2020				2021				2022			
	P	S	A	W	P	S	A	W	P	S	A	W	P	S	A	W
Permission ethics committees																
Ongoing recruitment of new sites																
Clinical study																
Database																
Interim statistical analysis																
Final statistical analyses																
Writing-up of results and manuscript																

P = spring, S = summer, A = autumn, W = winter

## Figures

### Inclusion criteria

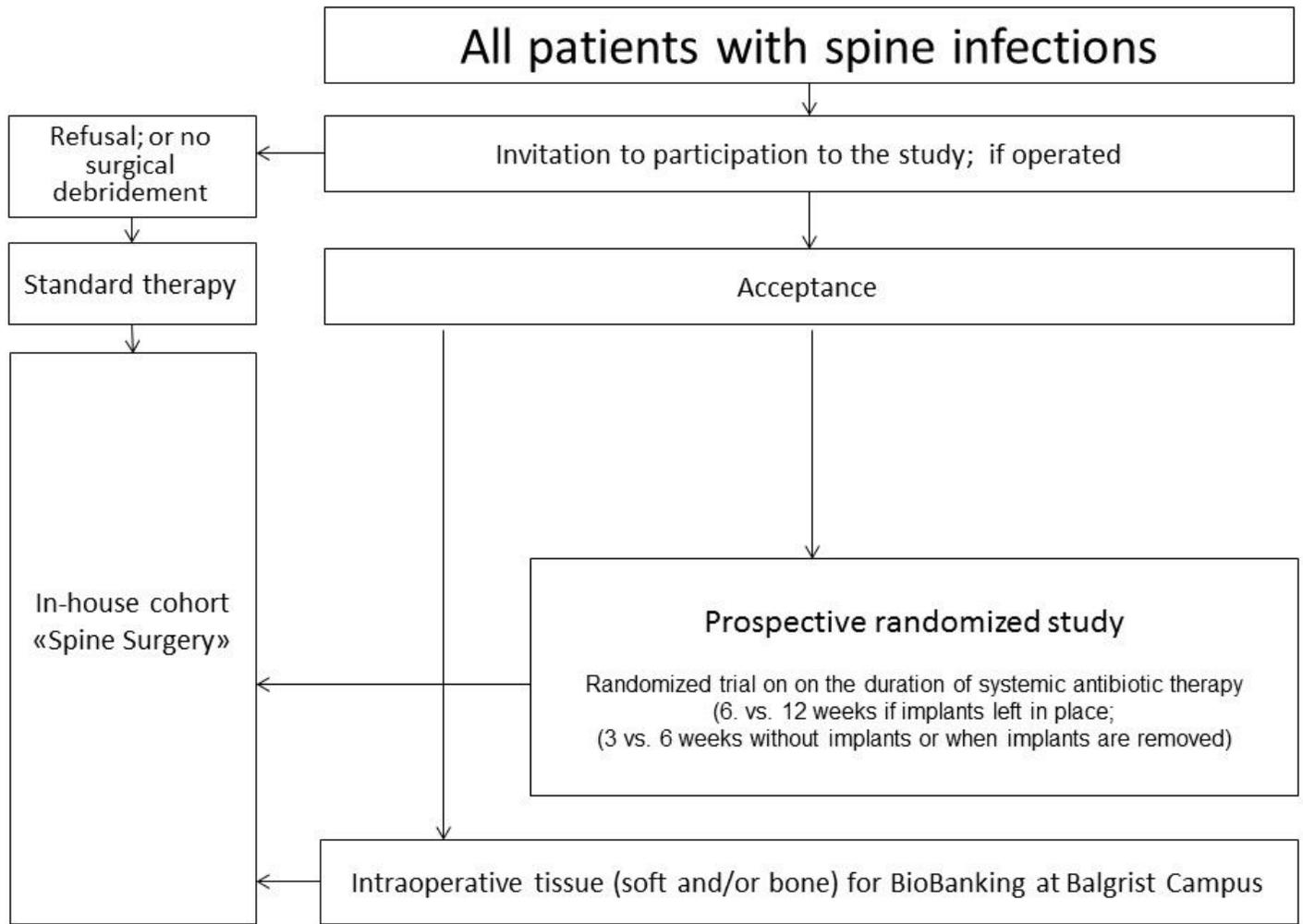
- Age  $\geq$  18 years
- Spine surgery and intraoperative debridement with any technique
- At least 12 months of scheduled follow-up from hospitalization
- Bacterial spine infection of any nature, independently of implants or comorbidities
- Previous (up to 96 hours) effective ongoing systemic antibiotic therapy for which the pathogens are susceptible
- Previous ineffective antibiotic therapy (resistant pathogens) for any duration

### Exclusion criteria

- Mycobacterial, fungal, nocardial, and actinomyces infections in the spine
- Non-resected cancer remaining in the infection site
- Bone marrow or recent solid organ transplant patient (Recent: <5 years)
- Any other infection requiring more than 6 weeks of antibiotic therapy
- More than three intraoperative debridements performed for any indication (infection, seroma, hematoma, material dislocations)
- Absence of at least one surgical intraoperative debridement for infection
- Previous effective and continuous systemic antibiotic therapy longer than 96 hours before debridement; unless there has been an antibiotic-free window for longer than 72 hours before debridement

## Figure 1

Study criteria



**Figure 2**

Study Flowchart

TIME-POINT**	STUDY PERIOD						
	Enrolment	Allocation	Study visits at hospital				Test-of-Cure Visit
	$-t_{1-4}$ and 0	0	V <sub>2</sub>	V <sub>3</sub>	V <sub>4</sub>	V <sub>5</sub>	V <sub>6</sub>
<b>ENROLMENT:</b>	X	X					
Eligibility screen	X	X					
Informed consent	X	X					
Allocation		X					
<b>INTERVENTIONS:</b>							
1. Implant-related spine infection			←—————→				
2. No infected implant			←—————→				
<b>ASSESSMENTS:</b>							
Baseline variables	X	X					
Control variables			X	X	X	X	
Outcome variables					X	X	X

**Visit times related to the Allocation (Inclusion) day:**

0 = start of therapy, V<sub>2</sub> = Day 15 (+/- 5 days; eventually EOT visit), V<sub>3</sub> = Day 21 (+/- 5 days), V<sub>4</sub> = Day 42 (+/- 5 days), V<sub>5</sub> = Day 84 (+/- 5 days), V<sub>6</sub> = End of treatment (EOT) visit - Day 21, 42 or 84 (+/- 5 days) (only if still receiving treatment after V<sub>4</sub>), V<sub>7</sub> (Test of cure (TOC) visit = approximately (+/- 60 days) at 12 months

**Baseline variables:** Patient’s general descriptive characteristics and general problems.

**Control variables:** Medical history and demographics. Determine the most appropriate route of administration (oral or IV) and empirical choice of the antibiotic. Outpatients will return to the clinic (assessments can be performed in the hospital for inpatients). Record any concomitant medications as well as any additional interventions required (except wound or bone debridement performed as part of standard care). Assess adverse events of long-term antibiotic therapy. Administer appropriate ulcer debridement and cleansing.

**Outcome variables:** Treatment variables, Administrative data, Outcome parameters. Nutritional status

Figure 3

SPIRIT-Chart of the enrolments and assessments during both randomized-controlled trials

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITchecklist.doc
- Table1.jpg