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STUDY PROTOCOL Open Access

Wound Infections Following Implant removal below the knee: the effect of antibiotic prophylaxis; the WIFI-trial, a multi-centre randomized controlled trial

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Abstract

Background: In the Netherlands about 18,000 procedures with implant removal are performed annually following open or closed reduction and fixation of fractures, of which 30-80% concern the foot, ankle and lower leg region. For clean surgical procedures, the rate of postoperative wound infections (POWI) should be less than ~2%. However, rates of 10-12% following implant removal have been reported, specifically after foot, ankle and lower leg fractures. Currently, surgeons individually decide if antibiotics prophylaxis is given, since no guideline exists. This leads to undesirable practice variation. The aim of the study is to assess the (cost-)effectiveness of a single intravenous gift of Cefazolin prior to implant removal following surgical fixation of foot, ankle and/or lower leg fractures.

Methods: This is a double-blind randomized controlled trial in patients scheduled for implant removal following a foot, ankle or lower leg fracture. Primary outcome is a POWI within 30 days after implant removal. Secondary outcomes are quality of life, functional outcome and costs at 30 days and 6 months after implant removal. With 2 x 250 patients a decrease in POWI rate from 10% to 3.3% (expected rate in clean-contaminated elective orthopaedic trauma procedures) can be detected (Power = 80%, 2-sided alpha = 5%, including 15% lost to follow up).

Discussion: If administration of prophylactic antibiotics prior to implant removal reduces the infectious complication rate, this will offer a strong argument to adopt this as standard practice of care. This will consequently lead to less physical and social disabilities and health care use. A preliminary, conservative estimation suggests yearly cost savings in the Netherlands of € 3.5 million per year.

Trial registration: This study is registered at Clinicaltrials.gov (NCT02225821) and the Netherlands Trial Register (NTR4393) and was granted permission by the Medical Ethical Review Committee of the Academic Medical Centre on October 7 2014.

Keywords: Antibiotic prophylaxis, Postoperative wound infection, Implant removal, Fracture surgery, Functional outcome

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Background

Open or closed reduction followed by internal fixation is a frequently performed operation for lower extremity fractures. Indications for implant removal in adult patients include symptomatic hardware (i.e. pain, thin overlying skin and restricted motion), implant failure (breakage, loosening), or a persistent infectious complication of the index procedure (infection or fistula). Following successful surgical procedures for extremity fractures, implant removal is not a routinely indicated procedure. However, removal of implants causing symptoms can result in pain relief and a high rate of patient satisfaction [1,2].

In the Netherlands about 18,000 implant removals are performed annually, of which 30-80% in the foot, ankle and lower leg region [3]. Literature on implant removal is sparse, but studies show most of the implants removed are following lower extremity injuries, especially below the knee (Table 1).

In addition, there is only a small amount of literature available on the risk of postoperative wound infection (POWI) following implant removal (Table 2). For 'clean' procedures the rate of POWI should be less than ~2% [11]. However, POWI rates of about 10-12%, specifically after foot, ankle and/or lower leg fractures, have been observed both by us and others in studies in which patients with implant removal due to an active wound infection were excluded [2,8]. In syndesmotic screw removal 9.2% of POWI were observed and in calcaneal implant removal following fracture surgery without postoperative complications in dislocated closed calcaneal fractures 19% of POWI were observed [9,10]. Preoperative prophylactic antibiotics might be beneficial to reduce the incidence of infectious complications following implant removal.

To date, only evidence exists on the effectiveness of prophylactic antibiotics in internal fixation with implants, but not in implant removal to prevent POWI [12]. In the Netherlands antibiotic prophylaxis is not routinely administered prior to implant removal as it is considered a clean procedure. Surgeons decide upon themselves if antibiotics are administered prior to implant removal, which is based on expert opinion as no evidence based guideline exists. This results in a undesirable practice variation.

Table 1 Studies on implant removal and the portion of implant removal from the foot-ankle and lower leg region

Study (year)	N of cases	N of IR FAL (%)
Raahave (1967) [4]	269	109 (41)
Richards (1992) [5]	88	25 (28)
Sanderson (1992) [6]	188	92 (49)
Minkowitz (2007) [7]	60	42 (70)
Vos (2012) [2]	284	89 (31)
Backes (2015) [8]	512	404 (79)

N; Number, *IR*; implant removal, *FAL*; foot- ankle or lower leg.

Table 2 Implant removal and incidence postoperative wound infections

Study (year)	N of cases	N of IR in FAL	N of POWI in FAL (%)
Raahave (1967) [4]	269	109	4 (3.7)
Richards (1992) [5]	88	25	0 (0)
Sanderson (1992) [6]	188	92	12 (13)
Minkowitz (2007) [7]	60	42	0 (0)
Schepers (2011) [9]	76	76	7 (9.2)
Backes (2013) [10]	228	69	6 (9)
Vos (2012) [2]	284	89	9 (11)
Backes (2015) [8]	512	403	49 (12.2)

N; Number, *IR*; implant removal *NA*; not available, *POWI*; postoperative wound infection, *FAL*; foot- ankle and lower leg.

Our aim is to study the (cost-)effectiveness of a single intravenous gift of Cefazolin prior to implant removal following surgical fixation of foot, ankle and/or lower leg fractures. The primary outcome is the incidence of POWI and secondary outcomes are health-related quality of life, functional outcome, health care utilization including transmural care, and costs from a health care and societal perspective.

Methods

This double blind randomised controlled trial will randomise between pre-operative administration of a single gift of Cefazolin or sodium chloride 0.9% in patients scheduled for elective implant removal below the knee. Twenty one centers will participate, including two Level 1 trauma centers.

Participants

The eligible study population will consist of all consecutive adult patients who are planned for elective implant removal following fracture treatment of the foot, ankle and/or lower leg.

Inclusion criteria

- Patients ≥18 years and ≤75 years of all ethnic backgrounds
- Scheduled implant removal following foot, ankle and/or lower leg surgery

Exclusion criteria

- Removal and adding osteosynthesis material during the same procedure

- Active wound infection or (plate) fistula
- Antibiotic treatment at the time of implant removal for a concomitant disease or infection
- A medical history of an allergic reaction to a cephalosporin, penicillin, or any other β-lactam antibiotic
- Known kidney disease (or known eGFR <60 ml/min/1.73 m^2)
- Pregnancy and lactation
- Immunosuppressant use in organ transplantation or rheumatoid joint disease

Interventions

After obtaining informed consent in the outpatient clinic, patients are contacted for a pre-operative assessment of functional status and health-related quality of life by way of self-administered questionnaires before surgery.

At the day of surgery, patients will be randomly assigned web-based in a 1:1 allocation ratio to one of the following study arms:

1. antibiotic prophylaxis: a single intravenous (iv) gift of 1000 mg Cefazolin in 10 cc of NaCl 0.9% (intervention group) or
2. no antibiotic prophylaxis: a single iv gift of 10 cc NaCl 0.9%.

After implant removal, patients are routinely assessed within four weeks postoperatively at the outpatient clinic (Figure 1). They are instructed to visit the outpatient clinic sooner in case of any signs of POWI, including

WIFI-trial	Enrollment	Allocation	Follow-up	
TIMEPOINT	$-t_1$ *Planning of surgery*	0	t_1 *4 weeks*	t_2 *6 months*
ENROLLMENT:	X	X		
Eligibility screen	X			
Informed consent	X			
Surgery		X		
INTERVENTION:		X		
Administration of AB prophylaxis		X		
ASSESSMENTS:	X		X	X
Incidence of POWI		←	—	→
EQ-5D-5L	X			X
LEFS	X			X
Patient satisfaction			X	X
iMCQ and iPCQ	X		X	X

Figure 1 Schedule of the study procedures. AB; antibiotic, POWI; postoperative wound infection, EQ-5D; EuroQuality of Life-5D, LEFS; Lower extremity functional Scale, iMCQ; iMTA Medical Consumption Questionnaire, iPCQ; MTA Productivity Cost Questionnaire.

warmth, redness, pain, swelling, drainage or a fever above 38.5 degrees Celsius. In case of a POWI, appropriate treatment is started according to protocol. In addition to the one time visit, the patient is asked to return a surgical wound healing post-discharge questionnaire by mail filled in at thirty days postoperatively. At six months after implant removal, patients are contacted by telephone or mail to fill out web-based questionnaires to assess functional outcome, QOL measurement, patient satisfaction, health care resources utilization, costs evaluation and questions on late infections (Figure 1).

Randomization

Randomization will be stratified per center and will be blocked within strata. Randomization sequence is generated by a dedicated computer randomization software program and will be performed preoperatively by a theatre assistant and/or the anaesthesiologist using a dedicated, password protected, SSL–encrypted website, ensuring allocation concealment during the Time Out Procedure. Given the randomization result, the anaesthesiologist will prepare either a syringe with 1000 mg Cefazolin or with NaCl 0.9% in the operating theatre or pre-operative holding area, which is administered thirty minutes prior to surgery through a peripheral iv catheter. The iv-catheter is used routinely for either sedatives, muscle relaxants and/or pain medication.

Blinding

Importantly, the anaesthesiologist prepares the study medication in the absence of the surgeon and administers the study medication or NaCl 0.9%. Neither the patient nor the surgeon will know if the patient receives prophylactic antibiotics. During the visit to the outpatient clinic the patient is seen by a physician other than the surgeon who performed the surgery. The attending physician will document signs of POWI and will determine its presence or any special findings on physical examination. In addition, a photograph of the wound(s) will be taken by the attending physician and kept in the medical charts. This will enable an independent outcome assessment committee to judge the clinical aspect of the surgical wound, blinded for the study intervention. If the local investigator or attending physician decides unblinding is essential, (s)he will make every effort to contact the coordinating investigator before unblinding to discuss options. Otherwise, the randomization code will be unblinded after analysis of the study results.

Primary Outcome

The primary outcome variable is a POWI within 30 days after implant removal as defined by the criteria applied by the CDC [11].

Secondary Outcomes

The study will focus on the following secondary outcomes (Figure 1):

- Health-related quality of life as measured by the EQ-5D questionnaire. The EQ-5D-5 L is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression [13].
- Functional outcome as assessed with the Lower Extremity Functional Scale (LEFS). The LEFS is a questionnaire containing 20 questions about a person's ability to perform everyday tasks and can be used to monitor the patient over time and to evaluate the effectiveness of an intervention [14,15].
- Patient satisfaction as measured by a ten-point Visual Analog Scale.
- Health care resources utilization (including amongst others, number of visits to the general practitioner and use of home care organizations) as measured by way of a combination of the Dutch iMTA Medical Consumption Questionnaire (iMCQ) and iMTA Productivity Cost Questionnaire (iPCQ).
- Costs (economic evaluation including budget impact analysis): the economic evaluation of antibiotic prophylaxis in patients scheduled for implant removal following a foot, ankle or lower leg fracture against no prophylaxis as its best alternative will be performed as a cost-effectiveness (CEA) as well as a cost-utility (CUA) analysis. The primary economic outcome in the CEA will be the costs per patient without a POWI, which closely relates to the clinical outcome measure. The CUA outcome is the costs per quality adjusted life year (QALY), which is a suitable outcome measure for priority setting during health care policy making across interventions, patient populations, and health care settings.

Sample size

Since information from prospective studies is limited, there is uncertainty about the POWI rate in current medical practice. In recent Dutch prospective studies the incidence of POWI below the knee is 11%, 12.2%, 9.2% and 19% [2,8-10]. To be on the safe side, a POWI rate of 10% is assumed for the control group. According to the expected rate in clean-contaminated elective orthopedic procedures, a POWI rate of 3.3% for the antibiotic prophylaxis group is assumed [11]. At least 216 patients per study arm are necessary to detect this difference with a power of 80% and a two-sided alpha of 5%. An estimation of the POWI rate in the control group is planned midway, when 216 patients have been included and reached the primary outcome at 30 days post-surgery. Since only an estimation of the POWI rate

of the control group is performed and no treatment effect is tested, the overall Type I error rate is maintained. This estimation will be performed by an independent statistician. To allow for an anticipated drop out of 10-15%, we will include a total of 250 patients per arm.

Based on our recent retrospective cohort studies in both an academic and non-academic hospital an annual number of 33–66 patients are expected to be included in our study for implant removal following lower leg injuries for each participating clinic [8]. With a number of 21 participating centers and an inclusion period of 1.5 years the number of study participants needed, is therefore highly feasible.

Statistical analysis

All analyses will be performed according to the intention-to-treat principle. In addition, protocol analyses will be done to check for robustness of results. A two-sided P-value < 0.05 will be considered statistically significant. In all analyses statistical uncertainties will be quantified using corresponding 95% two-sided confidence intervals. Descriptive analysis will be performed to compare baseline characteristics between patients with and without an infection. Univariate analysis will be performed for primary and secondary outcomes, followed by a multivariate logistic regression analysis to eliminate confounders. All analyses will be done using the Statistical Package for the Social Sciences (SPSS) version 19.0. (SPSS, Chicago, Illinois, USA).

Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 10, 64th WMA General Assembly, Forteleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and the Good Clinical Practice Guidelines (ICH-GCP).

Recruitment and consent

The patient will be informed about the WIFI-trial when he or she visits the outpatient clinic and implant removal is discussed. Documents are handed to the patient and the patient is asked to read the patient information letter. In order to be able to prepare for the elective (day care) surgery the patient is asked to participate in the trial during this visit to the outpatient clinic and will be asked to sign the informed consent form. Surgeons are asked by the coordinating investigator to check whether patients are included in the pre-operative assessment a day prior to surgery.

Benefits and risks assessment, group relatedness

Patient risks in this study are minimal and acceptable, as Cefazolin is currently used as prophylaxis in open reduction and internal fixation of fractures. Patients in both study groups will not be exposed to risks other than in current practice, since there is practice variation in the use of prophylactic antibiotics. As mentioned, currently surgeons decide upon themselves if antibiotics are administered preoperatively. We assume that the routine use of prophylactic antibiotics prior to implant removal following surgical fixation of foot, ankle and/or lower leg fractures will reduce the rate of POWI significantly (by two-thirds, from 10% to 3.3%). If our hypothesis is supported by the results of the proposed RCT, this will offer a strong argument to incorporate prophylactic use of a Cefazolin as strategy of choice in (inter)national guidelines for implant removal following fixation of ankle, foot and lower leg fractures. This could lead to less morbidity and social adverse effects in patients like pain, physical discomfort, multiple outpatient clinic visits/less healthcare consumption, work absenteeism and decreased self-confidence.

Indemnities

The institutional review board at the AMC has waived liability insurance, because no additional risk can be attributed to participation in this study.

Publication plan

The principal investigator, the study designer and the study coordinator will be named author. There will be a limit of ten authors. All others will obtain group authorship in the study group. All authors including group members are allowed to present the results.

Discussion

This RCT on wound infections following implant removal is performed in twenty-one different hospitals by a larger number of surgeons, which causes heterogeneity in patients and surgeons. However, we believe this also reflects normal practise in which antibiotic profylaxis could be beneficial. If our assumption that prophylactic antibiotics prior to implant removal reduces the infectious complication rate is confirmed by this RCT, this will offer a strong argument to adopt a single gift of antibiotic prophylaxis as standard practice of care. This will reduce the incidence of POWI and consequently will lead to less physical and social disabilities and health care use. In addition, it will decrease the rate of use of empiric broad-spectrum antibiotics (and antibiotic resistance) prescribed upon suspicion or diagnosis of a POWI. A preliminary, conservative estimation suggests yearly cost savings in the Netherlands of € 3.5 million per year.

Abbreviations

AB: Antibiotic; CEA: Cost-effectiveness analysis; CUA: Cost-utility analysis; EQ-5D: EuroQuality of Life-5D; FAL: Foot- ankle and lower leg; iMCQ: iMTA Medical Consumption Questionnaire; iPCQ: MTA Productivity Cost Questionnaire;

IR: Implant removal; Iv: Intravenous; LEFS: Lower extremity functional Scale; N: Number; NA: Not available; POWI: Postoperative wound infection; RCT: Randomized controlled trial; SPSS: Statistical Package for the Social Sciences; QALY: Quality adjusted life year; WIFI: Wound infections following implant removal.

Competing interests

The authors declare that they have no competing interests. Funding from ZonMw (Goed Gebruik Geneesmiddelen) was received for this study. ZonMw funds health research and stimulates use of the knowledge developed to help improve health and healthcare in the Netherlands.

Authors' contributions

All authors participated in the design of the study and the drafting of the manuscript. MB designed the study and drafted the manuscript, NWLS participated in the design of the study, helped the draft and critically revised the manuscript, JCG participated in the design of the study and critically revised the manuscript and TS designed the study, helped the draft and critically revised the manuscript. All other authors have critically revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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References

1. Williams AA, Witten DM, Duester R, Chou LB. The benefits of implant removal from the foot and ankle. J Bone Joint Surg Am. 2012;94(14):1316–20.
2. Vos DI. Implant removal after fracture healing. Facts and fiction. PhD thesis. Enschede: University Utrecht, Department of Surgery; 2013. Gildeprint Drukkerijen Enschede.
3. Vos D, Hanson B, Verhofstad M. Implant removal of osteosynthesis: The dutch practice. Results of a survey. J Trauma Manag Outcomes. 2012;6(1):6,2897. -6-6.
4. Raahave D. Postoperative wound infection after implant and removal of osteosynthetic material. Acta Orthop Scand. 1976;47(1):28–35.
5. Richards RH, Palmer JD, Clarke NM. Observations on removal of metal implants. Injury. 1992;23(1):25–8.
6. Sanderson PL, Ryan W, Turner PG. Complications of metalwork removal. Injury. 1992;23(1):29–30.
7. Minkowitz RB, Bhadsavle S, Walsh M, Egol KA. Removal of painful orthopaedic implants after fracture union. J Bone Joint Surg Am. 2007;89(9):1906–12.
8. Backes M, Schep NW, Luitse JS, Goslings JC, Schepers T. High rates of postoperative wound infection following elective implant removal. Under review.
9. Schepers T, Van Lieshout EM, de Vries MR, Van der Elst M. Complications of syndesmotic screw removal. Foot Ankle Int. 2011;32(11):1040–4.
10. Backes M, Schep NW, Luitse JS, Goslings JC, Schepers T. Indications for implant removal following intra-articular calcaneal fractures and subsequent complications. Foot Foot Ankle Int. 2013;34(11):1521–5. doi:10.1177/1071100713502466.
11. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Hospital infection control practices advisory committee. Infect Control Hosp Epidemiol. 1999;20(4):250,78. quiz 279–80.
12. Boxma H, Broekhuizen T, Patka P, Oosting H. Randomised controlled trial of single-dose antibiotic prophylaxis in surgical treatment of closed fractures: The Dutch trauma trial. Lancet. 1996;347(9009):1133–7.
13. Rabin R, de Charro F. EQ-5D: A measure of health status from the EuroQol group. Ann Med. 2001;33(5):337–43.
14. Binkley JM, Stratford PW, Lott SA, Riddle DL. The lower extremity functional scale (LEFS): Scale development, measurement properties, and clinical application. North american orthopaedic rehabilitation research network. Phys Ther. 1999;79(4):371–83.
15. Hoogeboom TJ, de Bie RA, den Broeder AA, van den Ende CH. The Dutch Lower Extremity Functional Scale was highly reliable, valid and responsive in individuals with hip/knee osteoarthritis: a validation study. BMC Musculoskelet Disord. 2012;13:117. doi:10.1186/1471-2474-13-117.

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RESEARCH PROTOCOL

Antibiotic prophylaxis to prevent **W**ound **I**nfections **F**ollowing **I**mplant removal after foot, ankle and lower leg fractures

PROTOCOL TITLE

'ANTIBIOTIC PROPHYLAXIS AND PREVENTION OF **W**OUND **I**NFECTIONS **F**OLLOWING **I**MPLANT REMOVAL AFTER FOOT, ANKLE AND LOWER LEG FRACTURES'.

Protocol ID	Antibiotic prophylaxis in foot, ankle and lower leg implant removal
Short title	WIFI-trial
EudraCT number	2014-000124-14
Version	5
Date	23-8-2016
Coordinating investigator	Coordinating investigator: Drs. M.Backes m.backes@amc.nl Phone: +31-6-14024227 Project leader: Dr. T. Schepers t.schepers@amc.nl Phone: +31-20-5669111
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Multicenter research	1. Academisch Medisch Centrum 2. Sint Lucas Andreas Ziekenhuis 3. Rijnland Ziekenhuis 4. Onze Lieve Vrouwe Gasthuis

	5. Ziekenhuis Amstelland 6. Flevoziekenhuis 7. BovenIJ Ziekenhuis 8. Tergooiziekenhuizen 9. MC Haaglanden 10. Bronovo 11. MC Zuiderzee 12. Westfries Gasthuis 13. Spaarne Gasthuis 14. Vlietland Ziekenhuis 15. Elkerliek Ziekenhuis 16. Amphia Ziekenhuis 17. Reinier de Graaf Ziekenhuis 18. Catharina Ziekenhuis 19. Deventer Ziekenhuis 20. VU Medisch Centrum 21. Gelre Ziekenhuizen 22. Medisch Centrum Alkmaar 23. Rode Kruis Ziekenhuis
Sponsor	Academic Medical Center, Amsterdam Trauma Unit, Department of Surgery
Subsidising party	AO Nederland
Independent expert (s)	Prof.dr. M.P. Schijven, surgeon

Laboratory sites	Department of Medical Microbiology Dr. I.J.M. Spijkerman, medical microbiologist
Pharmacy	Hospital Pharmacy Academic Medical Center Amsterdam Kenniscentrum Geneesmiddelenonderzoek

PROTOCOL SIGNATURE SHEET

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AB	**Antibiotics**
AE	**Adverse Event**
AR	**Adverse Reaction**
ASA	**American Society of Anaesthesiologists**
CA	**Competent Authority**
CDC	**Centres for Disease Control and Prevention**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CRF	**Case Report Form**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IR	**Implant Removal**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
FAL	**Foot, Ankle and Lower leg**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
POWI	**Postoperative Wound Infection**
QOL	**Quality of Life**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
WBP	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

In the Netherlands about 18,000 surgical procedures with implant removal are annually performed after fracture healing, of which 30-80% concern the foot, ankle and lower leg region. For clean surgical procedures, the rate of postoperative wound infections (POWIs) should be less than 5%. However, rates of 10-12% following implant removal, specifically after foot, ankle and lower leg fractures are reported. Currently, surgeons decide individually if antibiotics prophylaxis is given, since no guideline exists. This leads to undesirable practice variation.

Therefore, we propose a double-blind randomized controlled trial (RCT) in patients scheduled for implant removal following a foot, ankle or lower leg fracture, to assess the (cost-)effectiveness of a single gift of antibiotic prophylaxis. Primary outcome is a POWI within 30 days after implant removal. Secondary outcomes are quality of life, functional outcome at 30 days and 6 months after implant removal and costs.

With 2 x 250 patients a decrease in POWI from 10% to 3.3% (expected rate in clean-contaminated elective orthopedic trauma procedures) can be detected (Power=80%, 2-sided alpha=5%, including 15% lost to follow up).

If our assumption that prophylactic antibiotics prior to implant removal reduces the infectious complication rate is confirmed by our RCT, this will offer a strong argument to adopt a single gift of antibiotic prophylaxis as standard practice of care. This will reduce the incidence of POWIs and consequently will lead to less physical and social disabilities and health care use. In addition, it will decrease the rate of use of empiric broad-spectrum antibiotics (and antibiotic resistance) prescribed upon suspicion or diagnosis of a POWI. A preliminary, conservative estimation suggests yearly cost savings in the Netherlands of €3.5 million per year.

1. INTRODUCTION AND RATIONALE

Imagine: a year ago you broke your ankle and were operated on. Full recovery took many weeks. Now the plate is removed, supposedly a minor procedure. However, 3 days after the operation you get a wound infection, necessitating a hospital admission, a re-operation and antibiotics. The healing process takes several weeks, with all its inconveniences, like changing wound dressings and absence from work.
This research proposal is about prevention of such infections.

Implant removal
Patients with lower leg fractures are treated either conservatively with a cast or with the use of implants (osteosynthesis material) to restore anatomy and function. The implant can be removed at a later stage. The indications for implant removal in adult patients include symptomatic hardware (i.e. pain, thin overlying skin and restricted motion), failure of the implant (breakage, loosening), or a persistent infectious complication of the index procedure (infection or fistula). Some patients choose to have implants removed for no specific reason[1-3]. Following successful surgical procedures for extremity fractures, implant removal is generally not necessary or recommended by a physician. However, removal of implants causing symptoms can result in pain relief and a high rate of patient satisfaction[4]. Despite adverse events and sometimes disappointing results, 95% of the patients and 97% of the surgeons would decide to remove the implant again in retrospect[5]. After fracture healing removal of implants is safe with minimal risk[6]. In conclusion, patients with symptomatic implants generally benefit from implant removal.

In the Netherlands each year about 18,000 surgical implant removals are performed after fracture healing, of which 30-80% from the foot, ankle and lower leg region[7]. In the foot and ankle region the bones are more prominent due to the limited soft tissue coverage (as compared to other bones with extensive muscle coverage). Therefore the rates of implant removal are higher than in any other region of the body. For example, after plating of the fibula in ankle fractures the plates are removed in about 27-36% of patients[8,9] and following a calcaneal fracture almost 50% of patients have their implant removed[10,11].
This is also reflected in the literature when looking at studies on fracture implant removal in general. Although some these studies are slightly outdated, most of the implants removed are following lower extremity injuries, especially below the knee (Table 1).

Table 1. Studies on implant removal and the portion of implant removal from the foot-ankle and lower leg region.

Study (year)	**N of cases**	**N of IR lower extremity (%)**	**N of IR FAL (%)**
Raahave (1976) [12]	269	220 (82)	109 (41)
Richards (1992) [13]	88	64 (73)	25 (28)
Sanderson (1992) [14]	188	149 (79)	75 (40)
Minkowitz (2007) [6]	60	52 (87)	29 (48)
Vos (2013) [5]	284	142 (50)	89 (31)
Backes (2013) [15]	512	437 (85)	404 (79)

N; Number, IR; implant removal, FAL; foot- ankle or lower leg

Several retrospective studies performed by the applicants in different centres show higher rates of POWIs[15-17] than the accepted 5% seen in clean orthopaedic procedures [18-27]. In these studies patients with an active wound infection or plate fistula were excluded. In syndesmotic screw removal 9.2% of POWIs were seen and in calcaneal implant removal following fracture surgery in dislocated closed calcaneal fractures 10% of POWIs were seen[16,17]. Finally in 410 procedures with removal of implants below the knee joint the postoperative rate of wound infections was 12.2%[15] (Table 2). A recent prospective study showed a POWI percentage of 10% following implant removal[5].

There is small amount of literature available on the risk of a POWI following implant removal (Table 2).

Table 2. Implant removal and incidence postoperative wound infections.

Study (year)	**N of cases**	**N of IR lower extremity**	**N of POWI lower extremity (%)**	**N of IR in FAL**	**N of POWI in FAL (%)**
Raahave (1976) [12]	269	220	7 (3.2)	109	4 (3.7)
Richards (1992) [13]	88	64	0 (0)	NA	NA
Sanderson (1992) [14]	188	149	20 (13.4)	92	12 (13)
Minkowitz (2007) [6]	60	52	0 (0)	42	0 (0)
Vos (2013) [5]	284	142	14 (10)	89	9 (11)
Backes (2013) [15]	512	437	55 (12.6)	403	49 (12.2)

N; Number, IR; implant removal NA; not available, POWI; postoperative wound infection, FAL; foot- ankle and lower leg

Implant removal and antibiotic prophylaxis

There is no literature available on the use of prophylactic antibiotics prior to implant removal in order to prevent a POWI. There is information, however, on the use of prophylactic antibiotics in clean elective orthopedic foot, ankle and lower leg surgery. In this field, the incidence of a POWI varies between 0.26% and 4.8% (Table 3).

Table 3. Studies on postoperative wound infections following clean elective foot and ankle surgery.

Study (year)	**N of cases**	**N of POWI (%)**	**Comparing surgery with and without AB prophylaxis**	**Rates of POWI with versus without use of prophylaxis**
Pavel (1977)[18]	96	4 (4.2)	Yes	5.4% vs. 2.4%**
Miller (1983)[19]	1841	41 (2.2)	No	-
Reyes (1997)[20]	459	3 (0.65)	Yes	0.43% vs. 0.88**
Sticha (1998)[21]	100	1 (1)	No	-
Zgonis (2004)[22]	555	17 (3.1)	Yes	1.4% vs. 1.6%**
Dickemore (2005)[27]	265	4 (1.56)	Yes	0.0% vs. 1.56%**
Cichero (2009)[23]	3846	10 (0.26)	No	-
Maher (2009)[24]	917	18 (1.96)	No	-
Butterworth (2010)[25]	2387	74 (3.1)	No	-
Wukich (2011)[26]	1000	48 (4.8)*	No	-

N; Number, AB; antibiotic, POWI; postoperative wound infection
* Study on patients with diabetes mellitus, ** not significant

Postoperative wound infections

In surgical fracture fixation with metal implants (the index procedure that precedes hardware removal at a later stage) it is routine practice to administer antibiotic prophylaxis, partly as a result of the 'Dutch Trauma Trial'[28]. In this trial the incidence of superficial and deep POWIs was 8.3% with placebo as compared to 3.6% with prophylactic ceftriaxone ($p<0.001$). In contrast to surgical fracture fixation with metal implants, antibiotic prophylaxis is not routine practice prior to implant removal. This is because, according to the Centers for Disease Control and Prevention (CDC) classification of surgical wounds, implant removal is considered a 'clean' procedure[29]; surgical wounds are classified according to the bacterial contamination (Table 4).

Table 4. Classification of surgical wounds based on the degree of bacterial load and the percentage of surgical site infection with and without the use of prophylactic antibiotics[29].

Classification	Criteria	POWI without AB	POWI with AB
Class I: Clean	An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow non-penetrating (blunt) trauma should be included in this category if they meet the criteria.	1-2%	2.1%
Class II: Clean-contaminated	An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.	6-9%	3.3%
Class III: Contaminated	Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered are included in this category.	13-20%	6.4%
Class IV: Dirty/Infected	Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.	30-40%	

POWI; postoperative wound infection, AB; antibiotics

For 'clean' procedures the rate of POWIs should be less than ~2%[29]. However, rates of about 10-12% of POWIs, specifically after foot, ankle and/or lower leg fractures, have been observed both by us and others in studies in which patients with implant removal due to an active wound infection were excluded[5,15]. Consequently, preoperative antibiotics might be beneficial to reduce the incidence of infectious complications. Use of a single gift of prophylactic antibiotics has been shown to be as efficient as repeated prophylactic gifts in other types of surgery[30]. Moreover, a single gift is preferred since it avoids development of antibiotic resistance.

To date, there is no evidence on the use of prophylactic antibiotics prior to implant removal in order to prevent a POWI. In current practice, surgeons decide upon themselves if antibiotics are administered prior to implant removal, which is based on expert opinion as no evidence based guideline exists. This results in undesirable practice variation.

In light of the above, our objective is to study the (cost-)effectiveness of a single intravenous gift of antibiotic prophylaxis with a first generation cephalosporin prior to implant removal following surgical fixation of foot, ankle and/or lower leg fractures. We will examine the effects on the rate of POWIs (primary outcome), health-related quality of life, functional outcome, health care utilization, including transmural care, and costs from a health care and societal perspective (secondary outcomes).

2 OBJECTIVES

Study question:
What is the effect of a preoperative single gift of antibiotic prophylaxis on the incidence of wound infections following implant removal in foot, ankle and lower leg surgery?

The primary outcome is the incidence rate of POWI within 30 days after implant removal as defined by the criteria applied by the Centres for Disease Control and Prevention (CDC) and diagnosed by the attending physician.

Secondary outcomes are health-related quality of life, functional outcome, patient satisfaction, several treatment and health care consumption related items and costs.

Hypotheses:
We hypothesize that the incidence of wound infections following implant removal below the knee joint is lower in patients receiving a preoperative single gift of antibiotic prophylaxis compared to patients without a gift of antibiotic prophylaxis. Rates of POWIs with and without the use of a gift of prophylactic antibiotics are expected to be respectively 10% and 3.3% (see chapter 4.4).

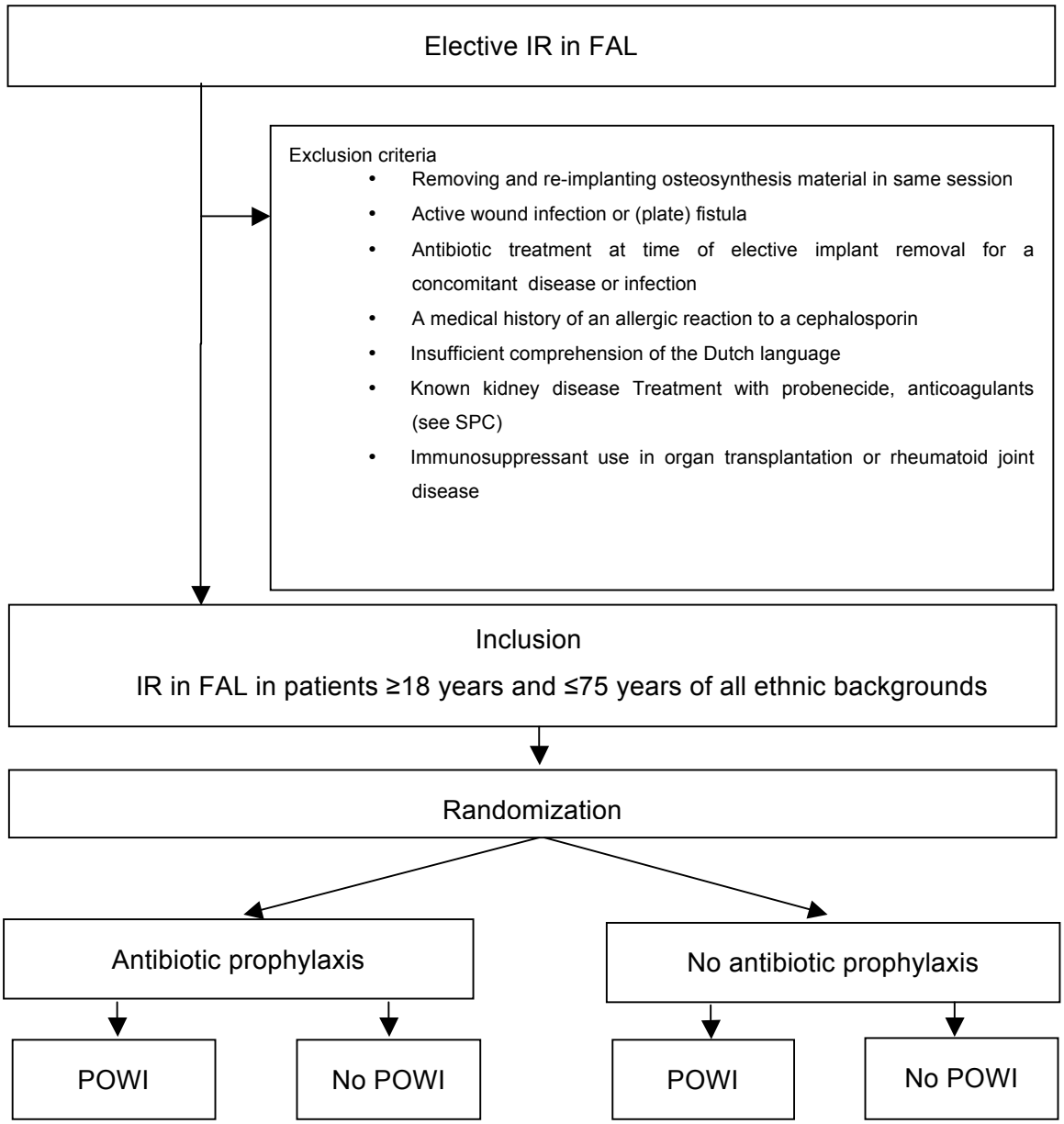
In addition, we expect a better functional outcome and quality of life following implant removal in patients without a POWI as compared to patients with a POWI.

Our primary aim is to supply scientific evidence for the use or non-use of antibiotic prophylaxis prior to implant removal. As a result we aim to create an evidence based guideline for all trauma and orthopaedic surgeons to guide prophylactic antibiotics use in the practice of implant removal in foot, ankle and lower leg surgery.

3 STUDY DESIGN

The study design is a multi-center, double-blind, randomized controlled trial. The duration of the study is estimated to be 30 months (Fig 1).

Figure 1. Flow chart of the study design.



IR; Implant removal, FAL; Foot, Ankle and Lower leg, POWI; postoperative wound infection

4. STUDY POPULATION

4.1 Population (base)

All patients aged between 18 and 75 years and scheduled for the removal of a metal implant following fracture surgery below the knee joint will be included upon obtaining informed consent.

4.2. Inclusion criteria

- Patients ≥18 years and ≤75 years of all ethnic backgrounds
- Implant removal following foot, ankle and/or lower leg surgery

4.3. Exclusion criteria

- Removing and re-implanting osteosynthesis material in the same session
- Active wound infection or (plate) fistula
- Antibiotic treatment at time of elective implant removal for a concomitant disease or infection
- A medical history of an allergic reaction to a cephalosporin
- Insufficient comprehension of the Dutch language to understand the patient information to make an informed decision to participate.
- Known kidney disease
- Treatment with probenecide, anticoagulants (see SPC)
- Immunosuppressant use in organ transplantation or rheumatoid joint disease

4.4. Sample size calculation

Since information from prospective studies is limited, there is uncertainty about the POWI rate in current medical practice. In a recent Dutch prospective study the incidence of POWIs is 11% below the knee and 10% in the lower extremity[5]. To be on the safe side, a POWI rate of 10% is assumed for the control group. According to the expected rate in clean-contaminated elective orthopaedic procedures[29], a POWI rate of 3.3% for the antibiotic prophylaxis group is assumed. At least 216 patients per study arm are necessary to detect this difference with a power of 80% and a two-sided alpha of 5%. To inform the sample size estimation and thus optimize study design, an estimation of the POWI rate in the control group is planned midway, i.e. when 216 patients have been included and reached the primary outcome at 30 days post-surgery. Since only an estimation of the POWI rate of the control group is performed and no treatment effect is

tested, the overall Type I error rate is maintained. To preserve the study blind, this estimation will be performed by an independent statistician. To allow for an anticipated drop out of 10-15%, we will include 250 patients per arm.

The participating centers have ample experience with implant removal after foot, ankle and lower leg fractures. They also all have experience in conducting RCTs and have proven to be reliable partners in recruiting patients for multicenter studies.
The number of participating centers can be increased if necessary.
Based on our recent retrospective cohort studies in both an academic and non-academic hospital an annual number of 33-66 patients are expected to be included in our study for implant removal for each participating clinic[15]. With a number of 23participating centers and an inclusion period of 1.5 years the number of study participants needed, is therefore highly feasible.

5. TREATMENT OF SUBJECTS

5.1. Investigational product/treatment

Implant removal with the use of a single prophylactic dose of cefazolin.

5.2. Use of co-intervention

Not applicable.

5.3. Escape medication

In case of an allergic response medical support is available. In case of convulsions administration of an anti-epileptic can be indicated. The primary goal when treating an allergic drug reaction is symptom relief. Symptoms such as rash, hives, and itching can often be controlled with antihistamines, and occasionally corticosteroids. For coughing and lung congestion, drugs called bronchodilators may be prescribed to widen the airways. For more serious anaphylactic symptoms (life-threatening allergic reactions including difficulty breathing or loss of consciousness) epinephrine may be given.

6. INVESTIGATIONAL PRODUCT

6.1. Name and description of investigational product(s)

Cefazolin, a first generation cephalosporin.

6.2. Summary of findings from non-clinical studies

See the Summary of Product Characteristics (SPC) (Appendix D2).

6.3. Summary of findings from clinical studies

See the SPC (Appendix D2).

6.4. Summary of known and potential risks and benefits

See the SPC (Appendix D2).

6.5. Description and justification of route of administration and dosage

Hundred twenty to fifteen minutes prior to the incision the patient will receive 1000 mg cefazolin solved in 10 cc of Sodiumchloride (NaCl) 0.9% or 10 cc of NaCl 0.9% through a peripheral intravenous (iv) catheter[31]. The iv-catheter is used for either sedatives, muscle relaxants and/or pain medication.

Use of a single gift of prophylactic antibiotics has been shown to be as efficient as repeated prophylactic gifts[30]. Moreover, a single gift is preferred since it avoids development of antibiotic resistance.

6.6. Dosages, dosage modifications and method of administration

A single gift of cefazolin 1000 mg solved in 10 cc of NaCl 0.9% or 10 cc of NaCl 0.9% will be administered intravenously. The dosage of cefalozin is based upon the advice in the national guideline of 'Stichting Werkgroep Antibioticabeleid' on antibiotic prophylaxis in trauma surgery[31,32].

6.7. Preparation and labelling of Investigational Medicinal Product

Cefazolin is supplied by the local hospital pharmacist and will be prepared for administration in the theatre or holding. Preparation and labelling is according to the local procedures.

6.8. Drug accountability

Drug accountability will be done according to the local protocol. In the Academic Medical Center a research investigator will guide the randomization or randomise in the theatre and show the randomization result to the anesthesiologist or assistant anesthesiology. The research investigator does not perform the surgery, is not part of the surgical team, nor does the postoperative follow-up. The anaesthesiologist will administer 1000 mg cefazolin solved in 10 cc of NaCl 0.9% or NaCl 0.9% following this randomization, 15-120 minutes preoperatively in the absence of the surgeon. In addition, the anesthesiologist will document the type of fluid administration and time of administration in their specific anaesthesiology file. This file is not easily accessible for the surgeon. Since the go-live EPIC the research investigator can order a 'HELP' order to be able to administer cefazolin or NaCl. To safeguard the double blind character of the study the operating surgeon is asked never to consult this specific anaesthesiology medical file by the trial coordinators and anaesthesiologist of duty. It is clearly explained to all the participating surgeons that this is required for the validation of the study. If, for any reason, they consult the 'HELP order' or the anaesthesiology file they will report this to the SC, who will report a protocol violation.

7. NON-INVESTIGATIONAL PRODUCT

7.1 Name and description of non-investigational product(s)

Not applicable.

7.2 Summary of findings from non-clinical studies

Not applicable.

7.3 Summary of findings from clinical studies

Not applicable.

7.4 Summary of known and potential risks and benefits

Not applicable.

7.5 Description and justification of route of administration and dosage

Not applicable.

7.6 Dosages, dosage modifications and method of administration

Not applicable.

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable.

7.8 Drug accountability

Not applicable.

8. METHODS

8.1. Study parameters/endpoints

8.1.1. Main study parameter/endpoint

The primary outcome variable is a POWI within 30 days after implant removal as defined by the criteria applied by the CDC (Table 5)[29].

Table 5. Criteria for defining a postoperative wound infection according to CDC criteria[29].

Superficial incisional postoperative wound infection: Infection occurs within 30 days after the operation and infection involves only skin or subcutaneous tissue of the incision and at least one of the following:	
1	Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2	Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3	At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.
4	Diagnosis of superficial incisional wound infection by the surgeon or attending physician.
Deep incisional postoperative wound infection: Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation and infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision and at least one of the following:	
1	Purulent drainage from the deep incision but not from the space component of the surgical site.
2	A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative.
3	An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4	Diagnosis of a deep incisional wound infection by a surgeon or attending physician.

8.1.2. Secondary study parameters/endpoints

The study will focus on the following secondary outcomes:

- Health-related quality of life at baseline, 1 month and 6 months after implant removal as measured by the EQ-5D questionnaire. The EQ-5D-5L is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression. It is primarily designed for self-completion by respondents and is ideally suited for use in postal surveys. It is cognitively simple, taking only a few minutes to complete (Appendix F1-1)[33].
- Functional outcome at baseline, 1 month and 6 months after implant removal as assessed with the Lower Extremity Functional Scale (LEFS). The LEFS is a questionnaire containing 20 questions about a person's ability to perform everyday tasks and can be used to monitor the patient over time and to evaluate the effectiveness of an intervention (Appendix F1-2)[34,35]. The LEFS can be used by

clinicians as a measure of patients' initial function, ongoing progress and outcome, as well as to set functional goals. The LEFS can be used to evaluate the functional impairment of a patient with a disorder of one or both lower extremities. It can be used to monitor the patient over time and to evaluate the effectiveness of an intervention[34].

- Patient satisfaction at 1 month and 6 months following implant removal as measured by a ten-point Visual Analog Scale (Appendix F1-3).

- Health care resources utilization at baseline, 1 month and 6 months after implant removal (including amongst others, number of visits to the general practitioner and use of home care organizations) as measured by way of a combination of the Dutch iMTA Medical Consumption Questionnaire (iMCQ) and iMTA Productivity Cost Questionnaire (iPCQ) (adapted to the study setting).

- Costs (economic evaluation including budget impact analysis, see Chapter 10): the economic evaluation of antibiotic prophylaxis in patients scheduled for implant removal (following a foot, ankle or lower leg fracture) against no prophylaxis as its best alternative will be performed as a cost-effectiveness (CEA) as well as a cost-utility (CUA) analysis. The primary economic outcome in the CEA will be the costs per patient free of POWI, which closely relates to the clinical outcome measure. The CUA outcome is the costs per quality adjusted life year (QALY), which is a suitable outcome measure for priority setting during health care policy making across interventions, patient populations, and health care settings.

8.1.3. Other study parameters

Patient, fracture and surgical characteristics will be documented.
Patient characteristics comprise age, gender, American Society of Anesthesiologists (ASA)-classification, substance abuse (smoking, alcohol, drugs) and medical history (including diabetes mellitus). Fracture characteristic comprise the type of fracture prior to osteosynthesis and the conditions of the soft tissues (open/closed). Surgical characteristics comprise type of hardware removal, complete or partial hardware removal, surgeon (resident, senior surgeon), duration of surgery, toe cover technique, use of a tourniquet, presence of bone overgrowth and wound closure technique.

8.2. Randomisation, blinding and treatment allocation

Patients will be randomly assigned in a 1:1 allocation ratio to one of the following study arms:

1) antibiotic prophylaxis: a single gift of 1000 mg cefazolin in 10 cc of NaCl 0.9% (intervention group) or

2) no antibiotic prophylaxis: a single gift of 10 cc NaCl 0.9%, given in the same manner (control group).

Randomization will be stratified by center and medical history of diabetes mellitus, since the latter is associated with an increased risk of a POWI[36]. Randomization will be blocked within strata. Randomisation sequence is generated by a dedicated computer randomisation software program, ensuring allocation concealment.

Randomization will be guided by or performed preoperatively by a research investigator using a dedicated, password protected, SSL–encrypted website. The research investigator does not perform the surgery, is not part of the surgical team, nor does the postoperative follow-up. Given the randomisation result, the anaesthesiologist will prepare either a syringe with 1000mg cefazolin or with NaCl 0.9% in the theatre or holding, which is administered 15-120 minutes prior to incision through a peripheral intravenous (iv) catheter. The iv-catheter is used routinely for either sedatives, muscle relaxants and/or pain medication. Importantly, the anaesthesiologist administers the study medication or NaCl 0.9% in the absence of the surgeon. Neither the patient nor the surgeon will know whether the patient receives prophylactic antibiotics. Unblinding is only performed in case of an allergic reaction during or within 24 hours following surgery or in emergency situations where knowledge of the administration of antibiotics is considered absolutely necessary for the clinical management of the subject. If the local investigator or attending physician decides unblinding is essential, (s)he will make every effort to contact the coordinating investigator before unblinding to discuss options. The randomisation code will be unblinded after analysis of the study results.

8.3. Study procedures

The study procedures are shown in Figure 2.

Figure 2. Schedule of the study procedures.

WIFI-trial	Enrollment	Allocation	Follow-up	
TIMEPOINT	$-t_1$ *Planning of surgery*	**0**	t_1 *4 weeks*	t_2 *6 months*
ENROLLMENT:	X	X		
Eligibility screen	X			
Informed consent	X			
Surgery		X		
INTERVENTION:		X		
Administration of AB prophylaxis		X		
ASSESSMENTS:	X		X	X
Incidence of POWI		◆———	◆———	◆
EQ-5D-5L	X			X
LEFS	X			X
Patient satisfaction			X	X
iMCQ and iPCQ	X		X	X

AB; antibiotic, POWI; postoperative wound infection, EQ-5D; EuroQuality of Life-5D, LEFS; Lower extremity functional Scale, iMCQ; iMTA Medical Consumption Questionnaire, iPCQ; MTA Productivity Cost Questionnaire

After informing the patient about the study and obtaining informed consent in the outpatient clinic, patients are contacted by the coordinating investigator for a pre-operative assessment of functional status and health-related quality of life by way of self-administered questionnaires prior to surgery. If a written informed consent is not obtained by the investigators prior to the preoperative assessment (questionnaires) an oral informed consent will be sufficient for this assessment. The signed consent is mandatory for randomization preoperatively. After implant removal, patients are seen within four weeks postoperatively at the outpatient clinic, as usual. Patients are instructed to visit the outpatient clinic sooner in case of any signs of a POWI: warmth, redness, pain, drainage or a fever above 38.5 degrees Celsius. During the visit to the outpatient clinic the patient

is seen by a physician other than the surgeon who performed the surgery. The attending physician will document signs of a POWI and will determine its presence or any special findings on physical examination. In addition, a photo will be taken by the attending physician and kept in the medical charts. This will enable an independent outcome assessment committee to judge the clinical aspect of the surgical wound, blinded for the study intervention. In case of a POWI, the appropriate treatment will be given as usual.

In addition to the questionnaires shown in Figure 2 the patient is asked to return a surgical wound healing post-discharge questionnaire by mail filled out at thirty days postoperatively (Appendix F1-3). Patients will receive a reminder by mail if the questionnaire is not completed after one week and have to complete the questionnaire within two weeks.
At six months after implant removal, patients are contacted by telephone to fill out self-administered questionnaires to assess functional outcome, QOL measurement, patient satisfaction, health care resources utilization, costs evaluation and questions on late infections (Appendix F1-1, F1-2, F1-3, F1-4 and F1-5).

8.4. Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

None.

8.5. Replacement of individual subjects after withdrawal

The number of patients who withdraw from the trial will be replaced by inclusion of a similar number of patients if the number of withdrawals before the assessment of the primary outcome exceeds the anticipated dropout rate of 15% allowed for in the sample size calculation. Our analysis will be according to the intention-to-treat principles to prevent a selective patient sample.

8.6. Follow-up of subjects withdrawn from treatment

Follow up of subjects withdrawn from treatment will be identical to follow up of included

subjects, since study follow up is identical to standard care. Withdrawn subjects will not receive further questionnaires.

8.7. Premature termination of the study

This study will be terminated prematurely if and when patients experience an amount of discomfort or adverse events that is disproportionate to the benefit of the study and presents too great a risk for the participating study subjects.

In case the study is ended prematurely, the coordinating PI will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

9. SAFETY REPORTING

9.1. Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

9.2. AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

The investigator will appreciate the severity of an event and give his opinion on whether the event is related or not to the study medication. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the study medication will be considered and investigated.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event) *(The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).*
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;

- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

NOTE: The following types of (prolongation of) hospitalisation are not considered to be a SAE:

- Any admission unrelated to an AE, e.g., for labour/delivery, cosmetic surgery, social and/or convenience admissions to a hospital;
- Protocol-specified admission, e.g., for a procedure required by the study protocol;
- Admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) **and** has not increased in severity or frequency as judged by the clinical investigator.

All SAEs that are identified from the time a subject consents to participate in the study until 24 hours following administration of study medication must be reported by the local site investigator/attending physician within 24 hrs to the coordinating investigator by email or telephone.

The coordinating PI or his delegate will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening (anaphylactic shock) should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

A predefined list of SAE's will be reported periodically instead of individually using the web portal *ToetsingOnlin*e. SAEs that will be listed and reported periodically are numerized in paragraph 4.8 of Appendix D2 and are as following: allergic response (erythema, urticaria, pruritis, angio-oedema), antibiotic-induced fever, headache, vertigo, paresthesia, convulsions, diarrhoea, nausea, vomiting, loss of appetite, abdominal pain, antibiotic-induced abnormalities in liver function tests (ASAT, ALAT, AF), reversible hepatitis, cholestatic icterus, kidney problems, flebitis and thromboflebitis.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The coordinating PI will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

The coordinating PI will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.2.3.1 Unblinding procedure for SUSARs

Breaking the code for SUSAR reporting is done by the attending physician by telephoning the coordinating investigator. See also paragraph 8.2.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs that are still ongoing at the end of the study period must be followed up to determine the final outcome.

Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately. For this study, the study treatment follow-up is defined as 24 hours following the last administration of study treatment.

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

This study is considered a low risk trial, since a commonly used antibiotic with a well known low risk profile is compared to standard care. Therefore, ongoing safety surveillance and interim safety analyses by a Data Safety Monitoring Board (DSMB)/Safety Committee are deemed not necessary.

10. STATISTICAL ANALYSIS

All analyses will be performed according to the intention-to-treat principle. In addition, per protocol analyses will be done to check for robustness of results. A two-sided P-value < 0.05 will be considered statistically significant. In all analyses statistical uncertainties will be quantified using corresponding 95% two-sided confidence intervals. All analyses will be done using the Statistical Package for the Social Sciences (SPSS) version 19.0. (SPSS, Chicago, Illinois, USA).

10.1 Primary study parameter(s)

The primary analysis will focus on the intention-to-treat comparison of the proportion of patients with a POWI within 30 days after implant removal in the two study treatment groups using the Chi-square statistic or Fisher's exact test as appropriate. The effect size will also be expressed in a crude relative risk estimate and absolute risk reduction. Additionally the primary outcome will be analyzed using multivariate logistic regression, adjusting for clinically relevant baseline imbalances and the stratifying variables.

10.2 Secondary study parameter(s)

Differences in the secondary outcome parameters between both treatment groups will be analysed using the two groups Student's t-test, Mann-Whitney U test, Chi-square test or Fisher's exact test when appropriate. In addition, multivariate logistic regression analysis for binary outcomes and linear regression analyses for continuous outcomes will be performed adjusting for clinically relevant baseline imbalances and the stratifying variables.

10.3 Other study parameters

Descriptive analyses will be performed for patient, fracture and surgical characteristics, using means and standard deviations, medians and interquartile ranges or counts and percentages, when appropriate. Differences between groups will be assessed using the two groups Student's t-test, Mann-Whitney U-test, Chi-square test or Fisher's exact test when appropriate.

10.4 Interim analysis

Since information from prospective studies is limited, there is uncertainty about the sample size assumptions. To inform the sample size estimation and thus optimize study

design, an estimation of the POWI rate in the control group is planned midway, i.e. when 216 patients have been included and reached the primary outcome at 30 days post-surgery. Since only an estimation of the POWI rate of the control group is performed and no treatment effect is tested, the overall Type I error rate is maintained. To preserve the study blind, this estimation will be performed by an independent statistician.

10.5 Economic analysis

The economic evaluation of antibiotic prophylaxis in patients scheduled for implant removal (following a foot, ankle or lower leg fracture) against no prophylaxis as its best alternative will be performed as a cost-effectiveness (CEA) as well as a cost-utility (CUA) analysis. The primary economic outcome in the CEA will be the costs per patient free of POWI, which closely relates to the clinical outcome measure. The CUA outcome is the costs per quality adjusted life year (QALY), which is a suitable outcome measure for priority setting during health care policy making across interventions, patient populations, and health care settings.Both analyses will be performed from a societal perspective with a time horizon of 6 months. Incremental cost-effectiveness ratios will be calculated reflecting the extra costs per additional patient free of POWI and the extra costs per QALY gained. Bias-corrected and accelerated non-parametric bootstrapping will be done to account for sampling variability. Results will be graphically displayed with quadrants of incremental costs versus effects and with cost-effectiveness acceptability curves showing the probability of a single gift of antibiotic prophylaxis being cost-effective at various levels of society's willingness to pay per QALY (range: 0-50,000 euro). Subgroups analyses will be performed for patients differing by age, sex, and location of the implant removal. Further sensitivity analyses will be done for uncertain parameters (e.g. unit costs of implant removal; ratio of superficial to deep POWI; length of the friction cost period) and with alternative cross-walk value sets to derive health utilities for international comparisons (see below). Scenario analyses will be performed with and without indirect non-medical costs. The costs of antibiotic resistance will be ignored, because development of resistance is rare with a single gift of antibiotic prophylaxis.

The costs will include the direct medical costs of antibiotics, surgery, wound care, other therapeutic procedures, diagnostic examinations, inpatient hospital stays (including day care treatment, if observed), out-patient hospital (e.g. orthopaedic surgeon) as well as out-of-hospital (e.g. physiotherapist) consultations, rehabilitation care, and home care. Further, the non-reimbursable, direct non-medical costs of informal care, over-the-counter medication and health related travel will be included. Finally, the indirect non-

medical costs of production loss at work (both, by absenteeism and presenteeism) will be included.

Data will be gathered by the clinical report forms and hospital information systems. Additionally, patients will be requested to complete a combination of the Dutch iMCQ and iPCQ (adapted to the study setting) at baseline and 1 and 6 months after randomization (respectively Appendix F1-4 and F1-5). Unit costing will conform to the most recent Dutch standard for costing in health care research in the year of reporting. In case of production losses, the friction costs approach will be applied. Yearly general consumer price-indices will be applied to transpose unit costs from different calendar years into the base year used for reporting purposes. Given the time horizon of 6 months no discounting of costs and effects will be done to account for time preferences.

The affordability of antibiotic prophylaxis for implant removal will be assessed from governmental and insurer perspectives following a budget impact analysis[37]. Such analyses may guide reimbursement decisions and influence volume and price negotiations between insurer and health care provider. In this study, the budget impact analyses will be incidence-based concerning new patients in the target population of the intervention. Linking costs to yearly population incidence data suffices to explore the impact on budgets. The governmental perspective is chosen to help setting priorities in health care optimization while simultaneously considering the wider implications of antibiotics prophylaxis for implant removal beyond the health care sector. The governmental perspective further includes an assessment of budget impact for premium financed health care. The insurer perspective is chosen to assess the net financial consequences of antibiotic prophylaxis on the demand for health care.

Against the base case scenario of no antibiotic prophylaxis we will assess alternative implementation scenarios of antibiotic prophylaxis: immediate, gradual (25% increase diffusion per year during the first four year) or partly (up to 50%) diffusion of antibiotic prophylaxis in the target population over time. Sensitivity analyses will be performed for the size of the target population over time, the observed uncertainty of prophylaxis being effective and the cost savings resulting from one prevented superficial or deep POWI.

The time horizon for all budget impact assessments will be 4 years and reported for each successive calendar year. For the budget impact analysis to be used for priority setting in health care, actual unit costing guidelines for costing in health care research will be applied. In case of impact assessments concerning premium financed health care and from the health insurer perspective, existing tariffs will be used.

11 ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 10, 64th WMA General Assembly, Forteleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and the Good Clinical Practice Guidelines (ICH-GCP).

11.2 Recruitment and consent

The patient will be informed about the WIFI-trial when he or she visits the outpatient clinic and the decision is made upon implant removal. Documents are handed to the patient and the patient is asked to read the patient information letter (Appendix E1). In order to be able to prepare for the elective day care surgery the patient is asked to participate in the trial during this visit to the outpatient clinic and will be asked to sign the informed consent form (Appendix E2).

Surgeons are asked by the coordinating investigator/project leader to check whether patients are included in the pre-operative assessment a day prior to surgery.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

11.4 Benefits and risks assessment, group relatedness

Patient risks in this study are minimal and acceptable, as cefazolin in currently used as prophylaxis in open reduction and internal fixation of lower leg, ankle and foot fractures. Participating patients in both study groups will not be exposed to risks other than in current practice, since there is practice variation in the use of prophylactic antibiotics.

At present, surgeons decide upon themselves if antibiotics are administered preoperatively, which is based on expert opinion as no evidence based guideline exists.

We assume that the routinely use of prophylactic antibiotics prior to implant removal following surgical fixation of foot, ankle and/or lower leg fractures will reduce the rate of POWIs significantly (by two-thirds, from 10% to 3.3%). If our hypothesis is supported by the results of the proposed RCT, this will offer a strong argument to incorporate prophylactic use of a cefazolin as strategy of choice in (inter)national guidelines for implant removal following fixation of ankle, foot and lower leg fractures.

This will reduce the incidence of POWIs and consequently will lead to less morbidity and social adverse effects in patients like pain, physical discomfort, multiple outpatient clinic visits/less healthcare consumption, work absenteeism and decreased self-confidence.
It will also decrease the rate of use of empiric broad-spectrum antibiotics often prescribed by the attending physician upon diagnosing a POWI. Therapeutic (not prophylactic) broad-spectrum antibiotics are responsible for the development of resistance whereas a single gift of prophylactic antibiotics of a first generation cephalosporin is not.
If the hypothesis of our study proposal proves to be true, it is preferred to administer prophylactic antibiotics to 100% of patients, instead of administering therapeutic antibiotics (among other treatments for POWI) to 10% of patients. The applicants believe a number needed to treat of 14.9 (100/(10-3.3)) is acceptable, considering the negative effects a POWI has on a patient (re-admission to hospital, re-operation, anesthesia, absence from work etcetera).
See also Chapter 13.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Subjects will not receive special incentives, compensation or treatment through participation in the study.

12 ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data collection will be by the use of CRF forms, prior to entry in an electronic GCP-proof database. Electronic data will be stored in two separate files. One data set will contain coded patient information and a second set medical history linked to these codes. The code will not be based on the patient initials and birth-date. The key to the code will be safeguarded by the coordinating investigator. Data will be stored and kept for fifteen years according to standard guidelines.

The handling of personal data will comply with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, WBP).

12.2 Monitoring and Quality Assurance

The study will be monitored according to ICH-GCP guidelines throughout its duration by (a) BROK or GCP-certified monitor(s) according to the Monitoring Plan (Appendix F4). The assigned monitor is not involved in the clinical trial as part of the trial site staff. The monitor's qualifications, including the received GCP-training, are documented.

The (Principal) Investigators will permit monitoring and make time available to meet with the monitor on a regular basis to discuss the progress of the study. Furthermore the Principal Investigator will only delegate trial related tasks to qualified persons.

The Sponsor's (or an authorized representative's) Quality Assurance department may conduct audits of all aspects of the clinical study either during the study or after the study has been completed. By participating in this trial the investigator agrees to this requirement. The clinical study may also be subject to inspection by regulatory authorities, the Health Care Inspectorate (IGZ, Inspectie voor de Gezondheidszorg), as well as the accredited Medical Ethical Committee/ Competent authority to ascertain that the study is being or has been conducted in accordance with protocol requirements, GCP, as well as the applicable regulatory requirements.

12.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;

- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor. (Examples of non-substantial amendments are typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted study documentation.)

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 End of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last telephone call in follow up.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.6 Public disclosure and publication policy

The study protocol will be published after approval of the study by the METC. The research data will be published, regardless of the outcome. Our trial will be registered in the CCMO register prior to the start of trial.

The Principal Investigator is author, the Project Leader is last author and the Coordinating Investigator will be first named author. There will be a limit of ten authors. All others will obtain group authorship in the study group. All authors including group members are allowed to present the results.

13 STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

Bacterial adhesion is the first and most important step in implant infection. It is a complex process influenced by environmental factors, bacterial properties, material surface properties and by the presence of serum or tissue proteins. Properties of the substrate, such as chemical composition of the material, surface charge, hydrophobicity, surface roughness and the presence of specific proteins at the surface, are all thought to be important in the initial cell attachment process. The biofilm mode of growth of infecting bacteria on an implant surface protects the organisms from the host immune system and antibiotic therapy[38]. To our knowledge no information is available on the pathophysiology causing a surgical site infection in hardware removal.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

It is common practice to administer antibiotic prophylaxis (intravenous cefalosporin) in patients in fracture surgery treated with open reconstruction and internal fixation with implants[28].

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Not applicable. As it is common practice to remove hardware material in humans there is no need for animal or ex-vivo models. In fracture surgery with placement of implants it is common practice to administer antibiotic prophylaxis. Therefore, in this field of surgery it is not new to consider antibiotic prophylaxis.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Cefazolin is a first generation cephalosporin with a broad antimicrobial activity against both Gram-positive and Gram-negative organisms. It interferes with the peptidoglycan synthesis of the bacterial wall by inhibiting the final transpeptidation needed for the cross-links. This effect is bactericidal. It has excellent in vitro activity against staphylococcal strains, streptococcal strains (other than enterococci), N. gonorrhoeae, H. influenzae and N. meningitidis. It also has excellent in vitro activity against members of the Enterobacteriaceae with the exception of Serratia and indole-positive Proteus. Ps. aeruginosa and B. fragilis are resistant. Clinical studies have shown to be effective

therapy for infections of soft tissue, respiratory tract, urinary tract, genital tract (caused by N. gonorrhoeae) and the central nervous system. Superinfections with Ps. aeruginosa and enterococcal strains may present a problem.

e. Analysis of potential effect

Cefazolin is relatively free of serious side effects. It is metabolically stable, and most of it is excreted unchanged in the urine. Three fourths of it are distributed in the extravascular compartment. Blood levels exceed the in vitro minimum inhibitory concentrations for many important gram negative pathogens.

Potentially adverse effects are allergic reactions, including rash, nasal congestion, cough, dry throat, eye irritation, or anaphylactic shock. Overdosage of cephalosporins can cause cerebral irritation leading to convulsions.

f. Pharmacokinetic considerations

The half-life is approximately 120 minutes following intravenous injection.

g. Study population

Research subjects are healthy individuals found eligible for elective surgery. As it is highly unlikely women with child bearing are planned for hardware removal these subjects are excluded.

h. Interaction with other products

Known pharmacological interactions are with amikacin, gentamycin, etilmicin and tobramycin which can cause and increased risk of nephrotoxicity. Probenecid may increase the serum level of cefazolin.

i. Predictability of effect

About 65-92% of cefazolin will be bound to plasmaproteins. Cefazolin has an excellent penetration in tissues, including muscles and bone tissue. Cefazolin is not metabolized and the majority is excreted through the glomeruli in de kidneys. A smaller amount is excreted in bile fluids.

j. Can effects be managed?

Patients are in the operating theatre under surveillance when cefazolin or NaCl 0.9% is administered. In case of an allergic response medical support is available. In case of convulsions administration of an anti-epileptic can be indicated.

13.2 Synthesis

The risks in this study are acceptable for the patients participating in this study, as cefazolin is already used as a prophylactic antibiotic in current practice in open reduction and internal fixation of lower leg, ankle and foot fractures. Patients in the non-antibiotic group will not be exposed to risks other than in current practice, since currently there is practice variation in the use of prophylactic antibiotics. Namely, surgeons decide upon themselves if antibiotics are administered preoperatively, which is based on expert opinion as no evidence based guideline exists.

The prolonged supervision of patients does not harm patients in any way and can only contribute to better patient management.

REFERENCES

1. Bostman O, Pihlajamaki H. Routine implant removal after fracture surgery: A potentially reducible consumer of hospital resources in trauma units. *J Trauma*. 1996;41(5):846-849.

2. Hanson B, van der Werken C, Stengel D. Surgeons' beliefs and perceptions about removal of orthopaedic implants. *BMC Musculoskelet Disord*. 2008;9:73-2474-9-73. doi: 10.1186/1471-2474-9-73; 10.1186/1471-2474-9-73.

3. Vos DI, Verhofstad MH, Hanson B, van der Graaf Y, van der Werken C. Clinical outcome of implant removal after fracture healing. design of a prospective multicentre clinical cohort study. *BMC Musculoskelet Disord*. 2012;13:147-2474-13-147. doi: 10.1186/1471-2474-13-147; 10.1186/1471-2474-13-147.

4. Williams AA, Witten DM, Duester R, Chou LB. The benefits of implant removal from the foot and ankle. *J Bone Joint Surg Am*. 2012;94(14):1316-1320. doi: 10.2106/JBJS.J.01756; 10.2106/JBJS.J.01756.

5. Vos DI, Verhofstad MHJ, Vroemen JPAM, et al. Clinical outcome of implant removal after fracture healing. results of a prospective multicentre clinical cohort study. *Submitted*.

6. Minkowitz RB, Bhadsavle S, Walsh M, Egol KA. Removal of painful orthopaedic implants after fracture union. *J Bone Joint Surg Am*. 2007;89(9):1906-1912. doi: 10.2106/JBJS.F.01536.

7. Vos D, Hanson B, Verhofstad M. Implant removal of osteosynthesis: The dutch practice. results of a survey. *J Trauma Manag Outcomes*. 2012;6(1):6-2897-6-6. doi: 10.1186/1752-2897-6-6; 10.1186/1752-2897-6-6.

8. Schepers T, Van Lieshout EM, De Vries MR, Van der Elst M. Increased rates of wound complications with locking plates in distal fibular fractures. *Injury*. 2011;42(10):1125-1129. doi: 10.1016/j.injury.2011.01.009; 10.1016/j.injury.2011.01.009.

9. Pot J, Van Wensen R, Olsman J. Hardware related pain and hardware removal after open reduction and internal fixation of ankle fractures. *The Foot and Ankle Online Journal*. 2011;4(5):1-6.

10. Harvey EJ, Grujic L, Early JS, Benirschke SK, Sangeorzan BJ. Morbidity associated with ORIF of intra-articular calcaneus fractures using a lateral approach. *Foot Ankle Int*. 2001;22(11):868-873.

11. Schepers T, Den Hartog D, Vogels LM, Van Lieshout EM. Extended lateral approach for intra-articular calcaneal fractures: An inverse relationship between surgeon experience and wound complications. *J Foot Ankle Surg*. 2013;52(2):167-171. doi: 10.1053/j.jfas.2012.11.009; 10.1053/j.jfas.2012.11.009.

12. Raahave D. Postoperative wound infection after implant and removal of osteosynthetic material. *Acta Orthop Scand*. 1976;47(1):28-35.

13. Richards RH, Palmer JD, Clarke NM. Observations on removal of metal implants. *Injury*. 1992;23(1):25-28.

14. Sanderson PL, Ryan W, Turner PG. Complications of metalwork removal. *Injury*. 1992;23(1):29-30.

15. Backes M, Schep NWL, Luitse JSK, Goslings JC, Schepers T. Risk factors and incidence of wound infections following implant removal. *In writing*.

16. Backes M, Schep NW, Luitse JS, Goslings JC, Schepers T. Indications for implant removal following intra-articular calcaneal fractures and subsequent complications. *Foot Ankle Int*. 2013. doi: 10.1177/1071100713502466.

17. Schepers T, Van Lieshout EM, de Vries MR, Van der Elst M. Complications of syndesmotic screw removal. *Foot Ankle Int*. 2011;32(11):1040-1044.

18. Pavel A, Smith RL, Ballard A, Larson IJ. Prophylactic antibiotics in elective orthopedic surgery: A prospective study of 1,591 cases. *South Med J*. 1977;70 Suppl 1:50-55.

19. Miller WA. Postoperative wound infection in foot and ankle surgery. *Foot Ankle*. 1983;4(2):102-104.

20. Reyes C, Barnauskas S, Hetherington V. Retrospective assessment of antibiotic and tourniquet use in an ambulatory surgery center. *J Foot Ankle Surg*. 1997;36(1):55-62.

21. Sticha RS, Swiriduk D, Wertheimer SJ. Prospective analysis of postoperative wound infections using an early exposure method of wound care. *J Foot Ankle Surg*. 1998;37(4):286-291.

22. Zgonis T, Jolly GP, Garbalosa JC. The efficacy of prophylactic intravenous antibiotics in elective foot and ankle surgery. *J Foot Ankle Surg*. 2004;43(2):97-103. doi: 10.1053/j.jfas.2004.01.003.

23. Cichero MJ. Elective foot and ankle surgery; activity and perioperative complications in queensland public hospitals, australia. *Foot (Edinb)*. 2009;19(3):139-144. doi: 10.1016/j.foot.2009.02.003; 10.1016/j.foot.2009.02.003.

24. Maher AJ, Metcalfe SA. A report of UK experience in 917 cases of day care foot surgery using a validated outcome tool. *Foot (Edinb)*. 2009;19(2):101-106. doi: 10.1016/j.foot.2009.01.002; 10.1016/j.foot.2009.01.002.

25. Butterworth P, Gilheany MF, Tinley P. Postoperative infection rates in foot and ankle surgery: A clinical audit of australian podiatric surgeons, january to december 2007. *Aust Health Rev*. 2010;34(2):180-185. doi: 10.1071/AH08687; 10.1071/AH08687.

26. Wukich DK, Lowery NJ, McMillen RL, Frykberg RG. Postoperative infection rates in foot and ankle surgery: A comparison of patients with and without diabetes mellitus. *J Bone Joint Surg Am*. 2010;92(2):287-295. doi: 10.2106/JBJS.I.00080; 10.2106/JBJS.I.00080.

27. Dickemore C, Green R, Jolley W, Green D. Prophylactic antibiotics in clean forefoot surgery: Are they necessary? the podiatry institute 2005. chapter 19. In: .

28. Boxma H, Broekhuizen T, Patka P, Oosting H. Randomised controlled trial of single-dose antibiotic prophylaxis in surgical treatment of closed fractures: The dutch trauma trial. *Lancet*. 1996;347(9009):1133-1137.

29. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. hospital infection control practices advisory committee. *Infect Control Hosp Epidemiol*. 1999;20(4):250-78; quiz 279-80. doi: 10.1086/501620.

30. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*. 2013;70(3):195-283. doi: 10.2146/ajhp120568 [doi].

31. Http://Swabid.nl/node/8738. .

32. van Kasteren ME, Gyssens IC, Kullberg BJ, Bruining HA, Stobberingh EE, Goris RJ. Optimizing antibiotics policy in the netherlands. V. SWAB guidelines for perioperative antibiotic prophylaxis. foundation antibiotics policy team. *Ned Tijdschr Geneeskd*. 2000;144(43):2049-2055.

33. Rabin R, de Charro F. EQ-5D: A measure of health status from the EuroQol group. *Ann Med*. 2001;33(5):337-343.

34. Binkley JM, Stratford PW, Lott SA, Riddle DL. The lower extremity functional scale (LEFS): Scale development, measurement properties, and clinical application. north american orthopaedic rehabilitation research network. *Phys Ther*. 1999;79(4):371-383.

35. Hoogeboom TJ, de Bie RA, den Broeder AA, van den Ende CH. The dutch lower extremity functional scale was highly reliable, valid and responsive in individuals with hip/knee osteoarthritis: A validation study. *BMC Musculoskelet Disord*. 2012;13:117-2474-13-117. doi: 10.1186/1471-2474-13-117 [doi].

36. Lilienfeld DE, Vlahov D, Tenney JH, McLaughlin JS. Obesity and diabetes as risk factors for postoperative wound infections after cardiac surgery. *Am J Infect Control*. 1988;16(1):3-6.

37. Mauskopf JA, Sullivan SD, Annemans L, et al. Principles of good practice for budget impact analysis: Report of the ISPOR task force on good research practices--budget impact analysis. *Value Health*. 2007;10(5):336-347. doi: VHE187 [pii].

38. Ribeiro M, Monteiro FJ, Ferraz MP. Infection of orthopedic implants with emphasis on bacterial adhesion process and techniques used in studying bacterial-material interactions. *Biomatter*. 2012;2(4):176-194. doi: 10.4161/biom.22905; 10.4161/biom.22905.