Spital Emmental Skin and Soft-Tissue Infection Pilot Study

Study Type:	Other Clinical Trial according to ClinO, Chapter 4
Risk Categorisation:	Risk category A to ClinO, Art. 61
Study Registration:	ISRCTN 15245496 SNCTP000003358
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Principal Investigator	Sponsor
Investigated Intervention:	Switch from intravenous to oral antibiotic treatment after 48 hours with the help of structured clinical criteria.
Protocol ID	2019-00558
Version and Date:	Version 4.1 (dated 18/11/2019)

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PROTOCOL SIGNATURE FORM

Study Title Spital Emmental Skin and Soft-Tissue Infection Pilot Study

Study ID ID 2019-00558

The Sponsor-Investigator has approved the protocol version 4.1 (dated 18/11/2019) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements.

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GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
ASR/DSUR	*Annual Safety Repot / Development Safety Report*
BASEC	*Business Administration System for Ethical Committees*
CRF	*Case Report Form*
CTCAE	*Common Terminology Criteria for Adverse Events*
FADP	*Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)*
eCRF	*electronic Case Report Form*
FOPH	*Federal Office of Public Health*
GCP	*Good Clinical Practice*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
ICH	*International Conference on Harmonisation*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
SAE	*Serious Adverse Event*
SSTI	*Skin and Soft-tissue infections*

1 STUDY SYNOPSIS

Not filled out the study synopsis because the finished protocol does not exceed 25 pages.

2 BACKGROUND AND RATIONALE

The Disease:
Erysipelas and cellulitis, designated as skin- and soft-tissue infections (SSTI), are among the most common community-acquired infections. SSTI is observed most frequently among middle-aged individuals and older adults. The incidence of SSTI is about 200 cases per 100'000 patient-years [1]. They manifest as an area of skin erythema, edema, and warmth; it develops as a result of bacterial entry via breaches in the skin barrier. The most common cause of SSTI is beta-hemolytic streptococci (73% in [2]), *and Staphylococcus aureus* [3]. Gram-negative aerobic bacilli are identified in a minority of cases. Even when no etiology is identified, the overall clinical response rate to beta-lactam antibiotic therapy is >95% [1]. Patients with non-purulent infection should be managed with empiric antibiotic therapy.

The Local Epidemiology:
The approach to empiric antimicrobial therapy includes consideration of local epidemiological factors. In our setting (Region of Emmental), the prevalence of MRSA is low, and beta-hemolytic streptococci are uniformly susceptible to penicillin.

The Dynamic of Inflammation Despite Antibiotics:
Patients with non-severe infection may be treated with oral antibiotics. The decision to initiate parenteral therapy should be based on individual clinical circumstances such as severity of clinical presentation and patient comorbidities. After initiation of parental therapy, antibiotic treatment may be switched to oral therapy, provided that there is a clinical response. Patients with cellulitis typically have symptomatic improvement within 24 to 48 hours of beginning antimicrobial therapy. Although, "visible" improvement of the erythema may take longer. A recent study showed that concordance between clinical and biochemical response was strongest at days 2 and 3. However, nonresponse at day 3 was a predictor of treatment duration >14 days, but *not* of clinical failure [4]. This indicates that biochemical (e.g.; C-reactive protein) or clinical variables (e.g.; size of erythema) may show a delayed response in comparison to the dynamic of bacterial killing. In other words, bacteria causing SSTI are killed early but the reduction of inflammation may take several days. Thus, a delayed clinical response is not or only rarely related to inappropriate therapy.

The Switch from Intravenous to Oral Antibiotic Treatment:
Early switch from intravenous to oral antibiotic therapy – without affecting the total antimicrobial treatment duration – may be a substantial benefit for both the patient and the health care system, as shown in a recent study on bone and joint infections [5]. To the best of our knowledge, there are no guidelines or uniformly accepted criteria on the duration of intravenous antibiotics prior to switch to oral formulation in SSTIs. Most clinicians use their clinical experience for decision making to switch from intravenous to oral antibiotic treatment. However, criteria for switching to oral antibiotics for various infectious diseases have been published previously [6-10], and proposed by the Institute for Infectious Diseases at the University of Bern [11]. The recommend total treatment duration for SSTIs ranges between 5 and 10 days [12].

The Study Idea and Rationale:
In this pilot study, patients with SSTI hospitalized at Spital Emmental and Spitalzentrum Biel will treated with intravenous antibiotics for maximum 48 hours. Then, selected patients according predefined criteria will be switched to oral therapy. It is a prerequisite that a predefined degree of clinical response must be noted. The study intends, as the name pilot study implies, production of data to justify a larger multi-center study. Nonetheless, it provides new scientific

input for the community, considering the effectiveness of short intravenous treatment duration in association to the presumed killing kinetics of bacteria involved in SSTI. In addition, the study addresses a relevant treatment question of a frequent infectious disease in clinical practice.

The Risk Categorization:
The median intravenous treatment duration for SSTI in a previous study was 3 (0 – 22) days [4]. Mild SSTI can be treated with oral formulation of antibiotics. Also, beta-hemolytic streptococci are highly susceptible to penicillin, with minimal inhibitory concentrations ranging considerably below 0.1 mg/L. As mentioned previously, and depending on the severity of SSTI, the infection can be treated with oral antibiotics only. Thus, our pilot study is embedded in practices of clinical routine and does not consist of any significant risk. The only 'intervention' consists of a structured decision making for a switch from intravenous to oral formulation of antibiotics within 48 hours, based on predefined criteria. In comparison, in clinical routine, this decision is taken individually on a day-by-day decision. Study patients will not be treated with different compounds or duration than patients not participating to the study. Blood sampling during hospitalization and duration of hospitalization is at the discretion of the responsible treating team. Therefore, the risk category for this research project is A according to art. 7 (HRO).

3 STUDY OBJECTIVES AND DESIGN

3.1 Hypothesis and primary objective

Hypothesis:
We hypothesize that intravenous antibiotic therapy for maximum 48 hours followed by oral formulation of antibiotic therapy (further designated as intervention arm) has the same clinical cure rate in SSTIs than

(i) a control group for comparison (duration of intravenous therapy not restricted and decided at the discretion of treating team, further designated as observation arm) and
(ii) reported in the literature for SSTIs (85% - 90% in [4]).

Objective:
The primary objective of the study is to estimate the efficacy of the antibiotic treatment concept in a pilot population.
The secondary objective of the study is to measure the duration of intravenous treatment in relation to the total antibiotic treatment duration in the intervention arm and in the observation arm, and to compare these results.

3.2 Primary and secondary endpoints

Primary endpoint:
The number cured cases will be measured as 'total number of treated cases' minus 'the number of failed cases'. Thus, the primary endpoint is 'absence of clinical failure'. Clinical failure is defined as increase in symptoms during antibiotic treatment or new course of antibiotics between end of therapy and 2 weeks after end of treatment or death or readmission for skin and soft tissue infection within 30 days of discharge [4].

The secondary endpoint:
The secondary endpoint is duration of intravenous treatment measured in number of doses and days of treatment.
The following baseline factors and parameters will be assessed at entrance and during treatment, respectively:

- Host variables: Age, sex, body mass index, allergies, comorbidities (cardiovascular), renal function, diabetes mellitus, insulin dependent, immunosuppression, cancer, alcohol consumption, IVDU.
- Clinical sepsis variables: pain at the site of infection, the presence of chills, body temperature, blood pressure (diastolic and systolic), heart frequency, O2-Saturation with or without oxygen.
- Referral dynamic variables: time from onset of symptoms to first physician contact, time from first physician contact to referral.
- SSTI variables: site of infection, size, color, portal of entrance, blisters
- Laboratory values (*only* if available and obtained at the discretion of the treating team): Hemoglobin, leukocytes, thrombocytes, creatinine, urea, ASAT, ALAT, bilirubin, alkaline phosphatase.
- Bacterial variables: Microorganism, minimal inhibitory concentration of antimicrobial compounds.
- Antibiotic variables: compound, dose, dosing scheme, application form, duration of treatment.

3.3 Study design

This is a prospective clinical trial. The switch from intravenous to oral treatment within 48 hours and - provided that predefined clinical and biochemical are fulfilled - is the intervention. Hence, there will be an "intervention arm" and an "observation arm."

Project design: This is a pilot study, with a clinical research approach. The project set-up is multicenter. It includes Spital Emmental with two study sites (Spital Burgdorf and Langnau) and Spitalzentrum Biel.

3.4. Study intervention

The planned intervention is the switch from intravenous to oral antibiotic treatment after 48 hours, provided that clinical criteria according to a predefined check list are fulfilled. The clinical criteria case report form (CRF Recruitment_15102019) is uploaded alongside this ethical proposal (CRF (Case Report Form)).

4 STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

The patient population: Adult (≥ 18 years old) presenting at the Spital Emmental or Spitalzentrum Biel with the diagnosis of SSTI.
Total number of participants: As this is a pilot study, we target 50 patients in the intervention arm. In addition, we aim to observe 50 patients without structured switch from intravenous to oral antibiotics for comparison (observation arm). On the basis of a retrospective survey in the two participating hospitals, we estimate that the study will be conducted within 18 months.
Inclusion criteria:

- Adult (≥ 18 years old) with SSTI
- Ability to understand and sign patient consent form
- Ability to consent for data use, or to consent for oral treatment, or to consent for both
- Not fulfilling exclusion criteria

Exclusion criteria:

- Not fulfilling inclusion criteria
- Not able to understand and sign patient consent form
- Denies participation in the study
- Received antibiotics 14 days or less prior to study inclusion

- Necrotizing fasciitis
- Septic shock or infection requiring intensive medicine care
- Impetigo without erysipelas or cellulitis
- Arthritis, Osteomyelitis, Tenosynovitis, Prosthetic Joint Infection, Foreign Body Infection
- Mastitis
- Non-bacterial infection or sterile skin inflammation
- Surgical site infections
- Skin abscess, bursitis,
- Diabetic Foot Infection PEDIS classification 3
- Bacteraemia with *Staphylococcus aureus* or *Pseudomonas aeruginosa*
- Ecthyma gangraenosum
- Gram-negative bacteria as causing organism for SSTI

Pregnant and lactating women can be included ONLY in the observation arm, and NOT in the intervention arm.

4.2 Recruitment, screening and informed consent procedure

The hospitals of recruitment: One centre with two sites (Spital Lagnau and Spital Burgdorf of Regionalspital Emmental AG) and one centre with one site (Spitalzentrum Biel).

Screening and recruitment: There will be consecutive ongoing recruitment through the study team in daily clinical practice. In both hospitals, there are daily meetings at which all new entries will be reported. Thereby, the study team can screen patients for study eligibility in case of erysipelas or cellulitis. The screening procedure is within routine/daily practice and can be performed every day. All screening procedure belong to routine or daily practice.

Information to eligible patients: The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he or she may withdraw from the study at any time and that withdrawal of consent will not affect his or her subsequent medical assistance and treatment. The participant will be informed that his or her medical records may be examined by authorised individuals other than their treating physician. There is no compensation or payments given to the project participants.

Patient consent: All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. Twenty-four hours will be given to the participant to decide whether to participate or not. Patients can actively refuse to be designated in the intervention arm but still participate in the observation arm, because this is a non-randomized pilot study. The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure. The consent form will be signed and dated by the investigator or his designee at the same time as the participant sign. A copy of the signed informed consent will be given to the study participant, and a copy added to the patient file. The consent form will be retained as part of the study records in a specifically designated folder in a lockable cupboard in the secretarial office. The secretarial office is located in a different area than the investigator's or his designee's offices. The informed consent process will be documented in the patient file and any discrepancy to the process described in the protocol will be explained.

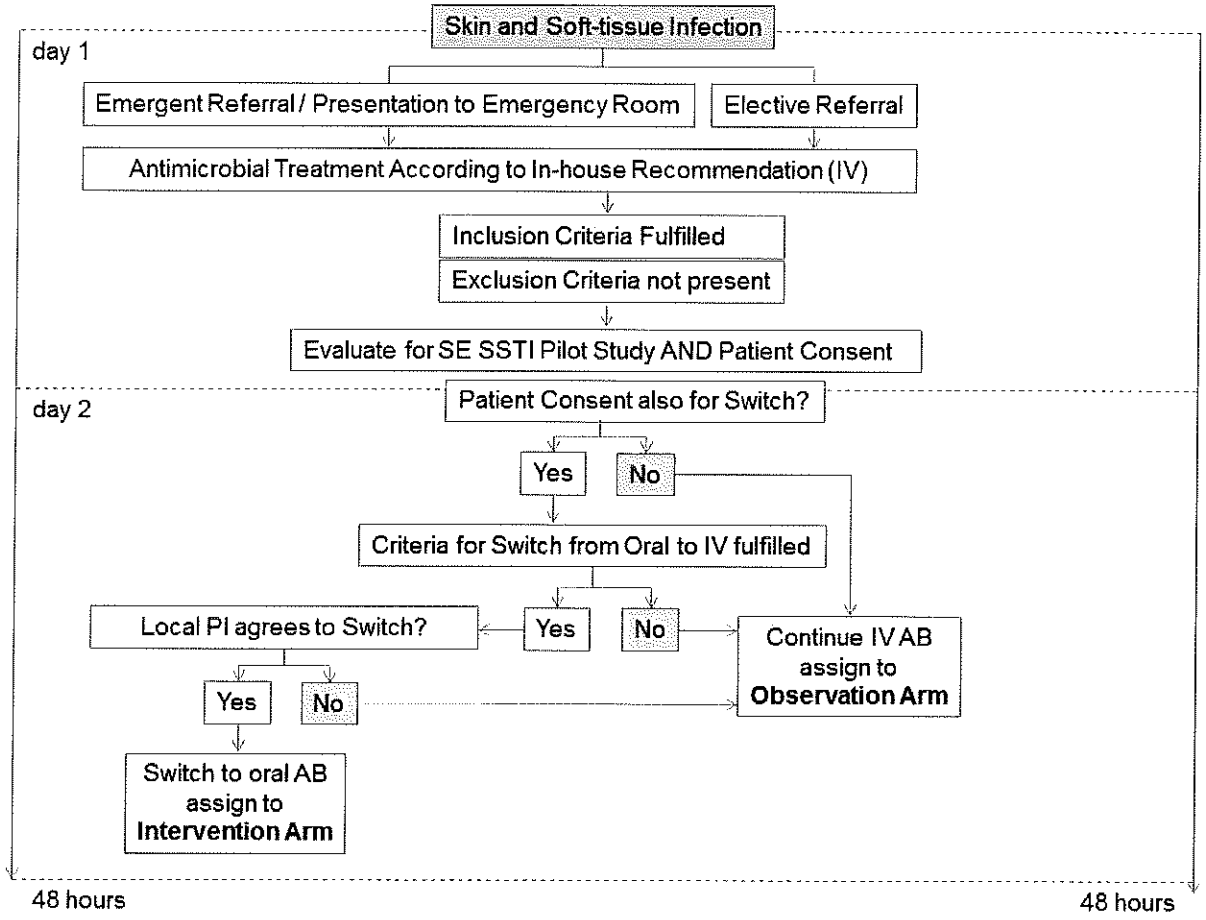

Figure 1: Study flow-chart

Intravenous antibiotics consists of Amoxicillin/Clavulanate 2.2 g every 8 hours. In case of allergies, cefuroxime 1.5 g every 8 hours *or* vancomycin 15 mg per KG body weight every 12 hours. All antibiotics compounds are used in clinical routine practice, irrespective of this study in the same doses.
Criteria for switch to oral treatment include clinical response to intravenous treatment, improvement of pain, improvement of erythema, diminishment of PEDIS 4 criteria, biochemical response (laboratory values), body temperature ≤37.8°C for at least 24 hours, ability to swallow pills, evidence of gastrointestinal absorption.
Oral antibiotics consists of Amoxicillin/Clavulanate 1g 3 times per day or Clindamycin 600mg 3 times per day. All antibiotics are used in clinical routine practice in the same doses.

4.3 Study procedures

The study flow-chart is illustrated in figure 1. The overall project duration, incl. recruitment period and poststudy analysis period is scheduled for 18 months. The project duration for each patient is 30 days. Clinical data are obtained at entrance, day 2, 4, and 6, as well as on day 30 via telephone contact. Laboratory investigations are ordered at the discretion of the treating physician. However, laboratory results will be obtained for the study, alongside to the closest date of clinical data. No specific procedure other than routine procedure is intended during hospitalization. A short telephone interview will be about the clinical recovery will be performed at day 30.

Data will be entered in a coded fashion in RedCap and stored at the server of the CTU. Bacteria isolated from the patient and responsible for the SSTI will be stored with labelled code at the Institute for Infectious Diseases of the University of Bern in a freezer at -80°C. The patient material alongside the bacteria will be stored. The labelling of the bacteria corresponds to the patient code for this study. A summary table listing all project visits including relevant procedures, sampling and timelines (i.e.; a schedule of assessment) is attached in appendix 2.

The pilot study consists of several biases, as alignment to a study group will be performed a study team, and thus can be overruled by the responsible physician. In addition, as this is a pilot study, alignment to an intervention arm will not be performed in a randomized fashion. However, the purpose of predefined criteria and a limit of maximum intravenous treatment duration of 48 hours is per se a measure to reduce these biases in clinical practice.

4.4 Withdrawal and discontinuation

Patients can withdraw consent from the study at any point of time and without justification. Patients will be withdrawn from the project if the disease progresses unexpectedly, if participant demonstrate considerable malcompliance or if exclusion criteria become apparent at a later point of time (i.e.; after primarily inclusion criteria were fulfilled). Upon withdrawal of informed consent, coded data will be used but then anonymized after the data analysis has been completed. Biological material (bacteria) will be stored and this material will not be destroyed in case of withdrawal but the labelling code will be anonymized.

5 STATISTICS AND METHODOLOGY

5.1. Statistical analysis plan and sample size calculation

Statistical analysis plan:

In a first step, we will perform descriptive statistics of all variables. We then will compare the proportions of the primary and secondary outcomes between the intervention arm and the observation arm. Categorical parameters will be compared with the χ^2 test or Fisher's exact test, and continuous variables will be compared with the Mann–Whitney *U* test or Kruskal–Wallis test. All analysis will be 2-tailed, and a *p* value <0.05 is considered statistically significant. Finally, we will perform multivariate analysis to find associations between patient variables outlined in 3.2 and secondary outcome.

Sample size calculation:

Considering the null hypothesis outlined in 2.1. (cure rate of SSTIs [85% - 90% in [4]), 902 patients (451 in each arm, two-sided alpha risk 5%, power 90%) would be necessary to reject the non-inferiority hypothesis of oral treatment after 48 hours in a clinical trial. As this is a pilot study, we aim for 50 patients in the intervention arm and 50 patients in the observation arm.

5.2. Handling of missing data and drop-outs

As this is a prospective clinical trial and in-hospitalized study, we estimate the proportion of missing data minor. However, missing data will be completed either by detailed chart review, interview with the treating team or patient. In case of persistent missing data, there are no means to replace the data, and missing data will be labelled as missed in the final analysis.

6 REGULATORY ASPECTS AND SAFETY

6.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the principles of Good Clinical Practice, the Human Research Act (HRA) and the

Human Research Ordinance (HRO) [1] as well as other locally relevant regulations. The Project Leader acknowledges his responsibilities as both the Project Leader and the Sponsor.

6.2 (Serious) Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation subject which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavorable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect

Both Investigator and Sponsor-Investigator make a causality assessment of the event to the trial intervention, (see table below based on the terms given in ICH E2A guidelines). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Both Investigator and Sponsor-Investigator make a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

Reporting of SAEs (see ClinO, Art. 63)

All SAEs are documented and reported immediately (within a maximum of 24 hours) to the Sponsor-Investigator of the study. If it cannot be excluded that the SAE occurring in Switzerland is attributable to the intervention under investigation, the Investigator reports it to the Ethics Committee via BASEC within 15 days. If the SAE occurs at one of the study sites, the coordinating Investigator reports the events to the Ethics Committee concerned, within 15 days.

Follow up of (Serious) Adverse Events

Patients will be monitored in acute care until resolution or stabilisation of signs and symptoms

related to SAEs. In outpatient care, patients will be followed-up weekly in the first month, every second week in the second month, and monthly thereafter until resolution or stabilisation.

6.3 Safety reporting

A safety report (ASR/DSUR) will be submitted to the local Ethics Committee by the Investigator once per year (ClinO, Art. 43 Abs).

6.4 Radiation

No radiation sources are used specifically for this study.

6.5 Pregnancy

In this study, reporting of pregnancies is not be necessary, since they will be not included in the intervention arm of the study (only observation arm), or they will be not included in the study.

6.6 Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.

Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of study site(s) or of study leader and sponsor (ClinO, Art. 29).

A list of all non-substantial amendments will be submitted to the competent EC together with the ASR once per year.

6.7 (Premature) termination of study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, e.g.

- Ethical concerns,
- Insufficient participant recruitment,
- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive),
- Alterations in accepted clinical practice that make the continuation of the study unwise, or
- Early evidence of harm or benefit of the experimental intervention

Upon regular study termination, the Ethics Committee is notified via BASEC within 90 days (ClinO, Art. 38).

Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38).

Upon project termination, the Ethics Committee is notified within 90 days. No biological material except isolated bacteria will be stored for this study at any time point. Health-related data will be stored in coded form. Upon project termination, a final report will be submitted to Ethics Committee within one year.

6.8 Insurance

For category A studies: In the event of study-related damage or injuries, the liability of the institution Spital Emmental provides compensation, except for claims that arise from misconduct

or gross negligence. Basler Versicherung: Betriebs-Haftpflichtversicherung für Spitäler (Versicherungsvertrag 30/3.988.151). Insurance of Spitalzentrum Biel (Versicherungsvertrag T80.2.457.425). Allianz, Bern.

7 FURTHER ASPECTS

7.1 Overall ethical considerations

As this is a pilot study, the generalizability of results is limited. However, it may justify a larger study. In addition, it may present a pioneer project for SSTI, and both physicians and patients may gain experience in handling a delayed clinical response despite early antibiotic effect. We see not additional burden and time effort for participants because the project is embedded in clinical practice and patients are treated equally, irrespective of whether they are in the intervention or observation arm. Patients in the intervention arm will be hospitalized and observed similar to those in the observation arm. Therefore, we feel that there an overall fair balance for the study participant.

7.2 Risk-benefit assessment

With our structured assessment after 48 hours, we estimate the risk of relapse or disease progression in the intervention arm as minor. This risk for study participants is further minimized because study participants remain hospitalized and are clinically examined daily. Conversely, patients without peripheral venous line or central venous line may develop complications of the catheter. The risk of a project includes the risks of the procedure itself (i.e.; being in a study). The risk of unauthorized data access and/or unwanted identification of project participants is minimized by coded patient ID, restriction of access to a small study team and storage of data in a password protected and access-trackable database (RedCap).

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

Project personnel are trained on all important project related aspects, including how to approach the patient, how to ask study participation and how to assess the clinical course. Data entry will be performed after training of the software. Data entry will be double viewed by PIs and confirmed. The sponsors and lead PI plans quality visits and regular data reviews. For quality assurance the sponsor, the Ethics Committee or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

8.2 Data recording and source data

Project data is recorded with an electronic Case Report Form via Redcap®. The list of the source data used in the project includes original records from the patient charts, clinical findings, observations and laboratory values (all outlined in 2.2), as well as patient responses from interviews in direct conversation (personal or telephone). All collected data are collected during the daily practice, also.

Data handling and record keeping / archiving / Data Management System (Hardware and software)

The CRFs in this trial are implemented electronically using a dedicated electronic data capturing (EDC) system (REDCap, https://www.project-redcap.org/). The EDC system is activated for the

trial only after successfully passing a formal test procedure. All data entered in the CRFs are stored on a Linux server in a dedicated mySQL database.
Responsibility for hosting the EDC system and the database lies with CTU Bern.

8.3 Confidentiality and coding

Trial and participant data will be handled with uttermost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other study specific documents, participants are only identified by a unique participant number.

The server hosting the EDC system and the database is kept in a locked server-room. Only the system administrators have direct access to the server and back-up tapes. A role concept with personal passwords (site investigator, statistician, monitor, administrator etc.) regulates permission for each user to use the system and database as he/she requires.
All data entered into the CRFs are transferred to the database using Transport Layer Security (TLS) encryption. Each data point has attributes attached to it identifying the user who entered it with the exact time and date. Retrospective alterations of data in the database are recorded in an audit table. Time, table, data field and altered value, and the person are recorded (audit trail).
A multi-level back-up system is implemented. Back-ups of the whole system including the database are run internally several times per day and on external tapes once a day. The back-up tapes are stored in a secure place in a different building.

Coding/Pseudonymization
e.g. Langnau patients 1-01, 1-02, 1-03, ... / Burgdorf patients 2-01, 2-02, 2-03, ... / Biel patients 3-01, 3-02, 3-03, ...
Study-related data of the patient will be collected in a coded manner. The names of the patients will not be disclosed. A code (unique, consecutive numbered per center) will be attributed to each patient registered.

The Key List / Random List
The code key list is kept in a locked cupboard at the secretary room of internal medicine. Members of the study team will not have access to the key (except PIs). One list for each site (Burgdorf, Langnau, Biel) will be generated.

8.4 Retention and destruction of study data and biological material

Archiving and Destruction (Analysis and archiving)
At final analyses, data files will be extracted from the database into statistical packages to be analyzed. After database lock, the status of the database is recorded in special archive tables. The sponsor will keep the Trial Master File, the extracted data, the meta data and interim/final reports for at least 10 years.

Electronic and Central Data Validation
Data is checked by the EDC system for completeness and plausibility. Furthermore, selected data points are cross-checked for plausibility with previously entered data for that participant. In addition, central data reviews will be performed on a regular basis to ensure completeness of the data collected and accuracy of the primary outcome data.
Before database lock the PI will validate the collected data with his signature.

Biological Material

No biological 'host' material from the patient will be stored. Isolated bacteria will be stored at the IFIK of the University of Bern at -80°C under SOP accredited regulations for 10 years.

The study data and bacteria may be used for a study in the future (further use). In such a scenario, approval from the corresponding EC will be requested prior to the start of the study.

9 MONITORIMG AND REGISTRATION

Monitoring duties will be performed by and under the responsibility of the PI not involved at the recruiting site (Prof. Dr. med. P. Sendi, IFIK). Regular monitoring visits at the investigator's site prior to the start and during the course of the study. Entered data in RedCap as well as patient consent form process and documentations in patient charts will be monitored.

Missing follow-up data will be collected via clinical or telephone contact with the patient or his/her GP at day 30 since onset of disease.

The source data/documents are accessible to monitors and questions are answered during by the local PIs and study team members during monitoring.

Registration in a national language in the Swiss National Clinical Trial Portal (SNCTP via BASEC) is performed. In addition, the study is registered in ISCTRN registry.

10. FUNDING / PUBLICATION / DECLARATION OF INTEREST

No specific funding is available for this study. It is an investigator initiated pilot study. The project is embedded within a medical dissertation. Hence, the results will be published either as a medical thesis at the website of the University of Bern (medical faculty) or as original manuscript in an international biomedical journal. There is no conflict of interests among the study team members.

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Appendix 1: Schedule of assessments

SE-SSTI	Entrance=day 1	Day 2	Day 4	Day 6	Discharge	Day 30
Visit	Information	Information Screening and 1st visit	2nd visit	3rd visit	4th visit	Phone call
check inclusion/ exclusion criteria	+	+				
oral and written Information		+				
Written consent		+				
Medical history		+				
Participant Characteristics		+				
Clinical finding/ evolution of SSTI	+	+	+	+	+	+
Laboratory Findings*	+	+	+	+	+	+
Microbiological Sampling	+					
Procedure		Switch from IV to oral ≤48h				
Questionnaire						+

*No laboratory tests are performed only because of the study. Laboratory tests are ordered the discretion of the physician, and will be obtained in the data bank if results are present. The laboratory results closest to the date of clinical investigation will be used.