University Hospital Basel

Division of Infectious Diseases
& Hospital Epidemiology
Hospital Epidemiology Department

PVP iodine vs Chlorhexidine in Alcohol for Disinfection of the Surgical Site: a cluster-randomized multicenter cross-over trial

Clinical Study Protocol

Study Type:	Prospective cluster-randomized multicenter cross-over trial
Study Categorisation:	Further use of non-genetic personal data with consent
Study Registration:	Intended ClinicalTrials.gov and SNCTP
Study Identifier:	PICASSo
Sponsor:	University Hospital Basel Petersgraben 4 4031 Basel
Sponsor-Investigator:	Prof. Dr. med. Andreas Widmer University Hospital Basel Division of Infectious Diseases and Hospital Epidemiology Petersgraben 4 4031 Basel Phone: +41 61 265 38 50 Email: andreas.widmer@usb.ch
Co-Investigators:	PD Dr. med. Jonas Marschall Inselspital Bern University Hospital Department of Infectious Diseases and Hospital Epidemiology Freiburgstrasse 15 3010 Bern Phone: +41 31 632 99 92 Email: jonas.marschall@insel.ch PD Dr. med. Stefan Kuster University Hospital Zurich Division of Infectious Diseases and Hospital Epidemiology Rämistrasse 100 / HAL14 C14 8091 Zürich Phone: +41 44 255 43 10 Email: stefan.kuster@usz.ch
Investigational Product:	Povidone Iodine 10% in solution (e.g. Braunoderm®)
Protocol Version and Date:	Version 2.0, July 3, 2018

CONFIDENTIAL

Signature Pages

Study number	Intended ClinicalTrials.gov and SNCTP
Study title	PVP iodine vs Chlorhexidine in Alcohol for disinfection of the Surgical Site: a cluster-randomized multicenter cross-over trial (PICASSo)

The Sponsor-Investigator and trial statistician have approved the protocol version 2.0, July 3, 2018, and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor-Investigator

Basel, 3.7.2018

Place/Date

Signature
Andreas Widmer, MD, MS, PI

Trial Statistician

Bern 20.7.18
Place/Date

A. Atk...
Signature
Andrew Atkinson, MSc

Local Principal Investigator at study sites:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site	University Hospital Zurich, Rämistrasse 100 / HAL14 C14, 8091 Zürich
Principal investigator	PD Dr. med. Stefan Kuster

Zuerich, July 5, 2018
Place/Date

Signature 

Site	Bern University Hospital, Freiburgstrasse 15, 3010 Bern
Principal investigator	PD Dr. med. Jonas Marschall

Bern, 11.7.2018 — Place/Date

Signature

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STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Prof. Dr. med. Andreas Widmer University Hospital Basel Division of Infectious Disease and Hospital Epidemiology Petersgraben 4 4031 Basel Phone: +41 61 265 38 50 Email: andreas.widmer@usb.ch
Study Title:	Polyvinylpyrrolidone iodine (PI) vs Chlorhexidine (CHX) in Alcohol for disinfection of the Surgical Site: a cluster-randomized multicenter cross-over trial
Short Title / Study ID:	PICASSo
Protocol Version and Date:	Version 2.0, July 3, 2018
Trial registration:	Intended ClinicalTrials.gov and Swiss National Clinical Trials Portal (SNCTP)
Study category and Rationale	Further use of non-genetic personal data with consent
Clinical Phase:	Clinical study phase 4
Background and Rationale:	Surgical site infections (SSIs) are the most common nosocomial infections in surgical patients causing significant increases in morbidity, mortality, and health care costs. As they are usually caused by components of the normal skin flora, disinfection of the surgical site with an antiseptic skin preparation is standard practice prior to any surgical intervention. The most commonly used disinfectants are either chlorhexidine in alcoholic solution (CHX) or PVP iodine in alcoholic solution (PI). Currently, the best compound for prevention of surgical site infections is unknown.
Objective(s):	The objective of our study is to prove non-inferiority of PI compared to CHX in preoperative skin antisepsis on the main outcome surgical site infection as defined by Swissnoso criteria and adapted to the National Nosocomial Infection Surveillance System (NNIS) score.
Outcome(s):	Primary outcome is crude proportion of patients with SSI, secondary outcomes are the proportion of SSI stratified for/adjusted for depth of SSI, type of surgery, and NNIS-score. Additional secondary outcomes are mortality rate and length of hospital stay. A risk factor analysis according to, duration of surgery, timing of antimicrobial prophylaxis, gender, Body Mass Index (BMI), and presence of implant in cardiac surgery will be performed. Safety outcomes are known side effects to either compound.
Study design:	Prospective cluster-randomized multicenter cross-over trial

Inclusion / Exclusion criteria:	Inclusion criteria: – male and female patients – aged ≥ 18 years – undergoing cardiac or certain types of abdominal surgery (colorectal surgery, cholecystectomy, herniotomy, appendectomy) at the study centers during the study period Exclusion criteria: – Contraindications to the use of either one of the compounds ▪ CHX: intolerance to any of the compounds of the preparation, application on cornea, wounds or mucosal membranes ▪ PI: Hyperthyroid disease, intolerance to any of the compounds, iodine allergy 2 weeks prior to radio-iodine-treatment, dermatitis herpetiformis duhring, application on cornea, wounds or mucosal membranes) – Emergency surgical intervention – Patients refusing general consent for use of personal data
Measurements and procedures:	We will include 1,527 patients in 2 strata: abdominal surgery and cardiothoracic surgery, summing up to 3,054 patients. The departments of surgery of the study sites will be randomized in clusters by month of surgical subspecialty to use CHX or PI. Follow-up by structured phone calls will be performed on day 30 (-50) and additionally on day 365 (- week 56) in case of cardiac surgery. This follow-up is routine for all patients for reasons of quality control and is not related to participation in the study.
Study Product / Intervention:	Preoperative skin disinfection with PVP-iodine with 10% iodine in alcoholic solution (such as: 1. Braunoderm®, B.Braun: Alcohol Isopropylicus 457,5 mg, Iodum 0,9 mg ut Povidonum Iodinatum, Excipiens ad solutionem per ml. 2. Betaseptic®, Mundipharma: Povidone iodine 32.4 mg, 389 mg isopropanole and 389 mg ethanol per ml)
Control Intervention:	Preoperative skin disinfection with CHX (Softasept® Chlorhexidin Lös 2% gefärbt, B Braun; composed of 20 mg chlorhexidine-digluconate and 0.7 ml ethanol per ml).
Number of Participants with Rationale:	We will include 1,527 patients in 2 strata: abdominal surgery and cardiothoracic surgery, summing up to 3,054 patients to achieve a power of 80% with a significance level of 5% accordingly to previous sample size calculation. We assume a 50:50 split between the types of surgery.
Study Duration:	26 months.

Study Schedule:	First-Participant-In: 8/2018 (planned) Last-Participant-Out: 10/2020 (planned)
Investigator(s):	Prof. Dr. med. Andreas Widmer University Hospital Basel Division of Infectious Diseases and Hospital Epidemiology Petersgraben 4 4031 Basel Phone: +41 61 265 38 50 Email: andreas.widmer@usb.ch PD Dr. med. Jonas Marschall University Hospital of Bern Division of Infectious Diseases and Hospital Epidemiology Freiburgstrasse 15 3010 Bern Phone: +41 31 632 99 92 Email: jonas.marschall@insel.ch PD Dr. med. Stefan Kuster University Hospital Zurich Division of Infectious Diseases and Hospital Epidemiology Rämistrasse 100 / HAL14 C14 8091 Zürich Phone: +41 44 255 43 10 Email: stefan.kuster@usz.ch
Study Centers:	Multicenter study involving three centers in Switzerland.
Statistical Considerations:	The study is designed to prove non-inferiority of PI to CHX in preoperative skin disinfection to prevent SSI. We define non-inferiority as overall proportion of SSI (cardiac and abdominal surgery) not exceeding plus / minus 2.5% (7.5 ± 2.5) based on the surveillance data of Swissnoso (data merge from November 2017). The primary data analyses follow the intention-to-treat principle. Descriptive and univariable statistics are used to characterize the study participants and to compare the baseline characteristics of the two groups. We compare the proportion of SSI and other categorical outcomes between groups using chi-square test. Sample-Size: Based on our experience with Swissnoso data we estimate the crude SSI-rate in cardiac surgery at 5% and in abdominal surgery at 10% adding up to an overall crude SSI-rate of 7.5%. We dimensioned the study to have 80% power at a significance level of 0.05 with a non-inferiority margin of 2.5%. According to the sample-size calculation, 1,374 patients are needed in each group. Assuming a maximum of 10% dropout from the trial, this would lead to a total sample size of 1,527 in each group, and 3,054 patients overall. Sample size calculated using “sealed envelope” website confirmed using R (package “TrialSize”, function “TwoSampleProportion.NIS”).

GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as all national legal and regulatory requirements.

ABBREVIATIONS

ANQ	National Association for Quality Development in Hospitals and Clinics
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
CA	Competent Authorities
CDC	Centers for Disease Control and Prevention
CEC	Competent Ethics Committee
CHOP	Swiss Operations Classification
CHX	Chlorhexidine in alcohol
CRP	C-reactive Protein
CTU	Clinical Trial Unit
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
IC	Informed Consent
ICH-GCP	International Conference on Harmonization-Good Clinical Practice
IDG	Informations- und Datenschutzgesetz Kanton Basel-Stadt, Schweiz (information and data protection act canton Basel, Switzerland)
IP	Infection Prevention
NHSN	National Healthcare Safety Network
NNIS	National Nosocomial Infections Surveillance System
OR	Operating Room
PI	PVP Iodine in alcohol
PVP	Polyvinylpyrrolidone
RCT	Randomized Controlled Trial
SNCTP	Swiss National Clinical Trials Portal
SSI	Surgical Site Infection
USB	University Hospital Basel
USZ	University Hospital Zurich
WHO	World Health Organization

STUDY SCHEDULE

	Study Period		
	Enrollment and Surgery	Post-Allocation	
Timepoint	Day of Surgery (DS) Day 0	Follow-up 1 (FU1) Day 30 (-50)	Follow-up 2 (FU2) Day 365 (week 56)
Enrollment			
Eligibility screen	x		
Generalized Informed consent (IC)	x		
Allocation	x		
Skin antisepsis	x		
Assessment			
Baseline characteristics*	x		
Outcome**		x	(x)

* Baseline characteristics:

1. Demographic data: sex, year of birth.
2. Clinical data: height, weight, BMI, American Society of Anesthesiologists (ASA)-score, presence of colorectal cancer for colorectal surgery, presence of diabetes mellitus, arterial hypertension, active smoking.
3. Operation data: time and type of surgery, duration of surgery, antimicrobial prophylaxis (antibiotic, dose, time of application), additional interventions, wound-contamination class according to the Centers for Disease Control and Prevention (CDC), exclusion criteria, side effects during application of product.
4. Laboratory values such as haemoglobin, leukocytes, creatinine, and CRP.

** Outcome:
Time of follow-up, status of patient, deceased (yes/no), reoperation (SSI/non-infectious complications), rehospitalization for SSI, SSI present, depth of SSI, time of diagnosis, microbiology results and if present responsible microorganism.

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Sponsor-Investigator

Prof. Dr. med. Andreas Widmer
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Prof. Andreas Widmer, together with his co-workers, was the leading figure in phrasing the scientific question of the current study as well as the design of the study. He will be responsible to ensure adequate collection, management, analysis and interpretation of the data. He will approve all final reports.

1.2 Principal Investigators

Trial site Basel:
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1.3 Statistician

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1.4 Monitoring institution

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Departement Klinische Forschung
c/o Universitätsspital Basel
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4031 Basel
Phone: +41 61 556 56 26

1.5 Data Safety Monitoring Committee

The sponsor investigator, principal investigators and trial statistician will form the data safety monitoring committee. The interim analysis is performed by the trial statistician.

1.6 Any other relevant Committee, Person, Organisation, Institution

Swissnoso
Sulgeneckstrasse 35
3007 Bern
Email: contact@swissnoso.ch

Swissnoso as Swiss society of hospital epidemiologists is responsible for data collection on surgical site infections (SSI) by official mandate from the National Association for Quality Development in

Hospitals and Clinics (ANQ). Swissnoso is also maintaining quality of data in their database situated at SwissRDL in Berne, Switzerland.

2. ETHICAL AND REGULATORY ASPECTS

The clinical study will only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities will be implemented.

2.1 Study registration

Registration in ClinicalTrials.gov as well as SNCTP is intended.

2.2 Categorisation of study

Further use of non-genetic personal data with consent.

2.3 Competent Ethics Committee (CEC)

The responsible investigators at each site ensure that approval by the Competent Ethics Committees (CEC) are sought prior to conduct of the clinical study. Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report will be submitted within one year after study end. Amendments are reported according to chapter 2.10. No changes are made to the study protocol without prior approval by the sponsor and CEC. Only exceptions may be apparent immediate hazards to study participants.

2.4 Competent Authorities (CA)

Not applicable.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki (1), the Guidelines of Good Clinical Practice (GCP) issued by ICH (2,3), the Swiss Law and Swiss regulatory authority's requirements (4,5,6). The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.6 Declaration of interest

None of the investigators has any financial interests in the results of this study. All applicants are employed in Swiss public hospitals and receive no industrial funding for this project. No patents or other means of commercialization are planned.

2.7 Patient Information and General Consent

All personal data registered in this trial is non-genetic and already collected in routine Swissnoso patient safety surveillance, and data on the antiseptic used, concomitant diseases (diabetes and hypertension, active smoking), laboratory values and side effects are recorded in the patient's history at the participating centers, irrespective of participation in this study. No additional study-specific data is collected.

All patients undergoing certain types of surgery at the participating centers are eligible for this study. They are included in the Swissnoso database according to the daily program of surgery at the centers. All patients are informed by means of brochures on the use of their data for scientific research in all the collaborating centers in form of a general consent. Additionally all patients are given an information leaflet on the nature of the routine Swissnoso SSI surveillance program. All data are already registered in routine Swissnoso patient safety surveillance or patient's history – irrespective of the participation in this study. Any changes during the study regarding the surveillance protocol by Swissnoso will also be applied to the study protocol.

Any patients refusing the general consent will be excluded from the study. The centers will control the patient histories prior to any data entry (at enrolment, on all follow-ups) and at the end of the study for any refusal and these patients will be excluded from the analysis of our study.
The randomization process of the intervention is not executed on a patient but on an institutional level using two different disinfectants, which are Swissmedic approved for preoperative skin antisepsis. Therefore, IC for each participant is not necessary. This randomization will be part of infection control guidelines issued by the participating centers.

2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and will comply with applicable privacy laws. Especially, anonymity of the participants will be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals. Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers to correspond to treatment data in the computer files. For data verification purposes, authorised representatives of the Sponsor, a competent authority, or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Early termination of the study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of superiority of one of the used disinfectants according to the interim analysis.

2.10 Protocol amendments

All substantial amendments must be read and approved by the Sponsor-Investigator prior to forwarding to CEC and CA, respectively. They are only implemented after approval of the CEC and CA respectively.
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 sponsor and the CEC/CA. Such deviations will be documented and reported to the sponsor and the CEC/CA as soon as possible.
All non-substantial amendments are communicated to the CA as soon as possible if applicable and to the CEC within the Annual Safety Report.

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Surgical site infections remain the most common nosocomial infection in surgical departments. Preparation of the skin by disinfectants belongs to the standards of care in surgery. Although the effectiveness of preoperative surgical site preparation is thought to be dependent on both the antiseptic agent used and the application method, it is not clear whether preoperative skin antisepsis actually reduces postoperative wound infection, and, if so, which antiseptic is most effective. The most widely used preoperative skin preparation agents include chlorhexidine gluconate and povidone-iodine solutions. As outlined below (point 3.4) the better one of the two components is not known yet. Therefore, a large trial including different types of surgery is urgently needed comparing the protective effect of CHX and PI.

3.2 Investigational Product (treatment, device) and Indication

PI is an iodine releasing disinfectant with remnant disinfecting activity and has been in use and Swissmedic approved for preoperative skin disinfection for decades. It has excellent activity against bacteria, fungi and different viruses. It has a rapid and lasting antibacterial effect. Main but rare side effects are allergic or cutaneous reactions. The compound used is composed of PVP-iodine with 10% iodine in alcoholic solution (products: 1. Braunoderm® by B.Braun: Alcohol Isopropylicus 457,5 mg, Iodum 0,9 mg ut Povidonum Iodinatum, Excipiens ad solutionem per ml. or 2. Betaseptic® by Mundipharma: Povidone iodine 32.4 mg, 389 mg isopropanole and 389 mg ethanol per ml).

3.3 Preclinical Evidence

Braunoderm®/ Betaseptic® and Softasept® Chlorhexidin Lös 2% gefärbt are approved by Swissmedic for preoperative skin disinfection.

3.4 Clinical Evidence to Date

Alcohol-based antiseptics with either chlorhexidine or iodine are better in terms of clinical and antimicrobial effectiveness than aqueous ones (7,8). The available evidence from 12 randomized controlled trials (RCTs) showed that for surgical site preparation of the skin alcoholic antiseptic solutions are more effective then aqueous solutions in reducing SSI (OR 0.60; 95% CI: 0.45 to 0.78) (7). A meta-analysis by the World Health Organization (WHO) published in 2016 (7) included six trials of chlorhexidine-alcohol versus iodine-alcohol preparations that showed significance in favour of chlorhexidine-alcohol. However, one trial included a solution with only 23% isopropanol in the iodine-alcohol group, which is clearly below the established microbicidal concentration range (about 50–90%, depending on alcohol species). Two other trials had unknown (and irretrievable) alcohol concentrations in their antiseptic preparations, and two further trials (adding up to five trials) had small sample sizes (n=100 each), leading to only one surgical site infection (9). The available evidence from these 5 RCTs showed that for surgical site preparation of the skin alcoholic PI is neither beneficial nor harmful in reducing SSI rate, when compared to alcoholic CHX (OR 0.60; 95% CI: 0.25 to 1.46) (10–14). After inclusion of an additional trial by Tuuli and colleagues (15) the final meta-analysis by the WHO included six trials of chlorhexidine-alcohol versus iodine-alcohol preparations that showed significance in favour of chlorhexidine-alcohol (OR 0.58; 95% CI: 0.42–0.80). Nevertheless, the SSI rate for CHX and PI reported by Tuuli was higher than in a large observational study from our institution even though the same definitions and follow-up procedures were applied (15). Due to the aforementioned critical issues of the final WHO recommendation, the meta-analysis was repeated after an updated literature search, excluding the trials with inadequate or unknown antiseptics and this updated analysis no longer showed chlorhexidine-alcohol to be

better than iodine-alcohol (9) Therefore, currently no solid evidence on superiority of either of the two routinely used compounds exists.

3.5 Dose Rationale / Medical Device: Rationale for the intended purpose in study (pre-market MD)

The products are used according to the manufacturers recommendations.

3.6 Explanation for choice of comparator (or placebo)

CHX as well as PI are the most commonly used preparations for preoperative skin antisepsis in Switzerland and worldwide. Both are deemed to be safe as well as effective for this purpose. As highlighted before, as of yet no robust evidence of superiority of either of the two preparations has been found. Therefore, a comparison of their effect on the major outcome of SSI is urgently needed.

3.7 Risks / Benefits

Risks:

The only randomized process in our trial is the type of disinfectant for preoperative skin disinfection. CHX as well as PI are both Swissmedic approved for this process. Patients with known contraindications to either compound and vulnerable patients are excluded from the study. In addition, an interim analysis (as described in section 11.4.4) will be performed after one year of study and in case of a clear superiority of one of the compounds, the study will be stopped and the institutions will return to their regularly used disinfection compound. Therefore, this proposed research project presents no more than minimal risk to the participants. There is minimal risk of violation of privacy protection, which is minimized by the study staff who works strictly according to ICH-GCP and IDG regulations.

Benefits:

There are no benefits to the individual participants. Nevertheless, as highlighted above, even after decades of use the best disinfection compound for preoperative skin antisepsis is not yet known. The current recommendation of the WHO to use CHX is only based on the results of one RCT whose results are not uniformly accepted by specialists in this issue. This trial will therefore demonstrate either superiority of one of the two compounds, or non-inferiority of either compound. This knowledge will shape the future of preoperative skin antisepsis for the prevention of SSIs and therefore will have a major impact on future patients undergoing surgery and their outcomes. The collected data will not be used for individual-related purposes and the results will be published without any correlation to the individual.

3.8 Justification of choice of study population

All patients not meeting exclusion criteria undergoing cardiac and certain types of abdominal surgery (colorectal surgery, cholecystectomy, herniotomy, appendectomy) at the study centers will be included in the analysis. The choice of surgeries is based upon the already existing surveillance system by Swissnoso and ANQ, thus reducing additional study visits for patients. As minors (aged < 18 years) and pregnant women, as well as patients undergoing emergency surgery are excluded, no vulnerable participants are included in the study. Inclusion of all patients will provide relevant insight of the impact of either two disinfection compounds for prevention of SSI in a not highly selected patient population.

4. STUDY OBJECTIVES

4.1 Overall Objective

To prove non-inferiority of PI to CHX for preoperative skin disinfection on surgical site infection in patients undergoing cardiac and abdominal surgery.

4.2 Primary Objective

Non-inferiority of PI to CHX for preoperative skin disinfection in terms of surgical site infections in patients undergoing cardiac or abdominal surgery.

4.3 Secondary Objectives

To investigate non-inferiority in terms of SSI in subgroups stratified by:

1. Surgical factors
   a. Type of SSI: superficial, deep, organ-space
   b. Type of surgery
   c. Timing of antimicrobial prophylaxis
   d. Duration of surgery
   e. Wound contamination class according to CDC
2. Patient factors
   a. Gender
   b. BMI
   c. Presence of implant (for cardiac surgery only)
   d. ASA score
   e. Presence of colorectal cancer for colorectal surgery
   f. Smoking, presence of diabetes mellitus, arterial hypertension, active smoking
   g. Laboratory parameters, such as hemoglobin, creatinine, leukocytes, CRP
3. NNIS score (combination of ASA score; wound contamination; duration of surgery)

4.4 Safety Objectives

To investigate the extent of side effects of either compound on the study population.

5. STUDY OUTCOMES

5.1 Primary Outcome

Primary outcome is presence of surgical site infection for abdominal and cardiac surgeries as defined by Swissnoso according to the National Healthcare Safety Network (NHSN) criteria. The occurrence of surgical site infections is evaluated at three time points:

1. At time of dismissal from the hospital
2. 30 days after abdominal and cardiac surgery
3. 1 year for cardiac surgery

The analysis will be performed using the final SSI rate (30 days for abdominal, 30 days/1 year for cardiac surgery) and according to the different types of infections. The infection ratio will be calculated as crude ratio as well as adapted to the NNIS score. The method of aggregation for the combined SSI rate for both types of surgery together will be a weighted average based on the proportion of SSIs from each surgery type.

5.2 Secondary Outcomes

Subgroup analysis stratified by:

1. Surgical factors
   a. Type of SSI: superficial, deep, organ-space
   b. Type of Surgery
   c. Timing of antimicrobial prophylaxis
   d. Duration of surgery,
   e. Wound contamination –class according to CDC
2. Patient factors
   a. Gender
   b. BMI
   c. presence of implant (for cardiac surgery only)
   d. ASA-score
   e. Presence of colorectal cancer for colorectal surgery
   f. Presence of diabetes mellitus, arterial hypertension, active smoking
3. Laboratory parameters such as hemoglobin, creatinine, leukocytes, CRPNNIS score (combination of ASA score; wound contamination; duration of surgery)
4. Mortality (in-hospital and 30 day for abdominal surgery; in-hospital, 30 day and 365 day for cardiac surgery), length of stay

5.3 Other Outcomes of Interest

Not applicable.

5.4 Safety Outcomes

Safety outcome variables include known side effects of the compounds as highlighted in point 3.2 mainly cutaneous reactions, which are very rare (< 1/1,000 for CHX, < 1/10,000 for PI).

6. STUDY DESIGN

6.1 General study design and justification of design

The data for this study will be based on routine collected data as part of further use research of this data. The intervention will be conducted as an open-label cluster-randomized cross-over multicenter trial with an allocation ratio of 1:1. Outcome variable is crude SSI rate, and the study is designed to prove non-inferiority of PI to CHX in preoperative skin disinfection to prevent SSI. We define non-inferiority as overall rate of SSI (cardiac and abdominal surgery not exceeding plus/minus 2.5% (7.5 ± 2.5) based on surveillance data of Swissnoso.
The departments of surgery of the study sites will be randomized centerwise in clusters by month to use CHX or PI. The products will be switched over according to the randomization. The primary data analysis follows the intention-to-treat principle.
Although randomization and allocation to the strata on a patient level may seem the method of choice, this is almost infeasible during routine work in the operating room (OR). Therefore, cluster-randomization is the best approximation to the ideal state.

6.2 Methods of minimizing bias

6.2.1 Randomization

A computer-generated randomization list will be generated. Each surgical study site will be randomized in clusters by month to use CHX or PI and will be switched over according to randomization as exemplary shown in table 1. The study nurse will provide the information which product must be used in the OR according to surgical subspecialty and hospital during the study month. A new randomization table will be generated in case the products are not available for > 1 week on the market, and the study will be halted during this phase. The allocation sequence will be generated by the main study nurse based on the computer-generated list. All respective surgical patients are eligible unless exclusion criteria are present or they refuse general IC. Patients are allocated by month, department, and subspecialty in this cluster-randomized trial.

	Month											
	1	2	3	4	5	6	7	8	9	10	11	12
Site 1	CHX	CHX	PI	PI	CHX	PI	CHX	PI	PI	PI	CHX	CHX
Site 2	PI	CHX	PI	CHX	PI	PI	CHX	CHX	CHX	PI	PI	CHX
Site 3	PI	PI	CHX	CHX	PI	CHX	PI	CHX	CHX	PI	PI	CHX

Table 1: Example for cluster randomization on site level.

6.2.2 Blinding procedures

The responsible statisticians are blinded to the allocation, personnel in the OR responsible for performing skin disinfection will not be blinded as both disinfectants are easily distinguishable by their color. This is also relevant for safety reasons in clinical routine. In addition, Infection Prevention (IP-) nurses responsible for follow-up and assessment of SSI may not be completely blinded to allocation of patients.

6.2.3 Other methods of minimizing bias

Not applicable.

6.3 Unblinding Procedures (Code break)

Not applicable for this study design.

7. STUDY POPULATION

7.1 Eligibility criteria

See synopsis.

7.2 Recruitment and screening

All patients undergoing cardiac or any of the aforementioned abdominal surgeries at any of the three study sites will be eligible for this study unless they meet exclusion criteria. As this is a cluster-randomized study, randomization will be at the level of the study site, and all patients will be treated according to the current randomization status. The postoperative surveillance of SSIs is already part of the common process in all patients undergoing certain surgical procedures at the study site for reasons of quality control. Therefore, no additional measures for recruitment are needed, and currently, both products belong to standard of care in Switzerland.

7.3 Assignment to study groups

Due to the process of cluster-randomization patients will not be directly randomized, rather the departments of surgery and surgical subspecialties will be assigned to either the CHX- or PI group. Patients undergoing surgery in these units will indirectly be assigned to either study group.

7.4 Criteria for withdrawal / discontinuation of participants

Due to the short nature of the intervention skin disinfection lasting only minutes no withdrawal from the intervention is feasible. Withdrawal of general consent will be recorded in the electronic Case Report Form (eCRF) and patients withdrawn from the analysis.

8. STUDY INTERVENTION

8.1 Identity of Investigational Products (treatment / medical device)

In principle, there are four study groups:

1. Cardiothoracic surgery – PI disinfection
2. Cardiothoracic surgery – CHX disinfection
3. Abdominal surgery – PI disinfection
4. Abdominal surgery – CHX disinfection

No other study specific interventions are planned.

8.1.1 Experimental Intervention (treatment / medical device)

As described in section 3.2.

8.1.2 Control Intervention (standard/routine/comparator treatment / medical device)

Chlorhexidine in alcohol (Softasept® Chlorhexidin Lös 2% gefärbt, from B. Braun Medical AG) is a cationic biguanide and exerts rapid and lasting disinfecting properties against bacteria, fungi, and certain viruses. It is composed of 20 mg chlorhexidine-digluconate and 0.7 ml ethanol per ml. Main but rare side effects (< 1/1,000) are dermal or allergic reactions.

8.1.3 Packaging, Labelling and Supply (re-supply)

All products are available commercially.

8.1.4 Storage Conditions

Supply, storage and return according to standard procedures of the hospital pharmacies of the study centers.

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

PI (Braunoderm® from B.Braun or Betaseptic® from Mundipharma) is applied prior to surgery on the patient's skin with the use of swabs. The product is applied three times. The cumulative residence time is a minimum of 3 minutes. The application is performed according to standard procedures of the participating centers and according to manufacturer's recommendations.

8.2.2 Control Intervention

CHX (Softasept® Chlorhexidin Lös 2% gefärbt, from B. Braun Medical AG) is applied three times on the patient's skin with the use of swabs. The cumulative residence time is a minimum of 3 minutes. The application is performed according to standard procedures of the participating centers and according to manufacturer's recommendations.

8.3 Dose / Device modifications

Not applicable.

8.4 Compliance with study intervention

As the application of antisepsis prior to surgery is limited to a few minutes, compliance on the patient level is guaranteed. On the institutional level, the randomization of the products will be part of the hospital guidelines and health-care workers have to adhere to it. The study nurse will monitor the

surveillance team to ensure follow-up of > 90% of patients. In addition, standardized observations of the disinfection process in the study sites will be taking place in at least two disinfection processes per week in each center using an application developed by Swissnoso (form uploaded to BASEC). These observations are also part of routine clinical monitoring for quality control.

8.5 Data Collection and Follow-up for withdrawn participants

Not applicable.

8.6 Trial specific preventive measures

There are no trial specific preventive measures and no restrictions. All patients are otherwise treated to the best standard of medical care.

8.7 Concomitant Interventions (treatments)

As skin antisepsis is the only intervention the medical care for all participating patients is according to the best medical knowledge of the participating centers. Additional measures to prevent SSIs are mainly antimicrobial prophylaxis, which is also recorded in the eCRF (prophylaxis yes or no, type of antibiotic, time of application, dose, and re-dosing of antibiotic if necessary).

8.8 Study Drug / Medical Device Accountability

The study drugs are shipped to and stored by the hospital pharmacies, according to their standard operation procedures.

8.9 Return or Destruction of Study Drug / Medical Device

Not applicable.

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments

As described in study schedule on page 14.

9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

Assessment of SSIs is following Swissnoso standard procedures and comprises a routine surveillance for means of quality control in all participating centers, irrespective of participation in this study. In brief, IP nurses supervised by infectious diseases specialists or other physicians without hierarchical link with the departments of surgery are in charge of the surveillance in each participating hospital. Surgeons are not allowed in the decision process of detecting SSIs. All IP nurses must attend a one-day special training course before starting surveillance. SSIs are diagnosed according to the Centers for Diseases Control and Prevention (CDC) definitions and classified as superficial incisional, deep incisional or organ/space infections. Patients are followed-up by IP nurses during their hospital stay and post-discharge after 30 (-50) days and additionally after 365 days (-56 weeks) in case of cardiac surgery. Any suspicion of SSI or unclear situation is presented to the supervising physician for decision about the diagnosis of SSI. The post-discharge follow-up is done performed by IP nurses through standardized phone interviews with the patients. At least five telephone attempts must be documented before a patient can be considered as lost-to-follow-up. Six questions are asked about unplanned medical visits, re-hospitalization, antibiotic prescription, and clinical symptoms of infection. Any suspected or unclear case triggers further contacts with the family or hospital physician to gather any available additional information.
Data recorded includes time of diagnosis, diagnostic criteria according to NNIS, extent of infection (superficial, deep, organ/space), and responsible microorganism if known. All data will be recorded on eRCF.

9.2.2 Assessment of secondary outcomes

The data of secondary outcomes (5.2) are systematically assessed and available for all patients undergoing surgery at the participating institutions.
They are recorded using the hospital medical records of the patients during hospitalisation.

9.2.3 Assessment of other outcomes of interest

Not applicable.

9.2.4 Assessment of safety outcomes

9.2.4.1 Side effects

Side effects will be recorded in the patient's history and routinely checked by IP nurses upon entry of patient's data in the database. It will be recorded separately in the eCRF.

9.2.4.2 Laboratory parameters

Not applicable.

9.2.4.3 Vital signs

Not applicable.

9.2.5 Assessments in participants who prematurely stop the study

Not applicable.

9.3 Procedures at each routine visit

9.3.1 Day of surgery/enrolment (DS, Day 0)

Day of surgery, allocation to intervention group according to cluster randomization. Inclusion into study as soon as surgery performed. Entry of baseline data into database (within 5 days after surgery):

1. Demographic data: sex, year of birth.
2. Clinical data: height, weight, BMI, ASA score, presence of colorectal cancer for colorectal surgery, presence of diabetes mellitus or hypertension, active smoking.
3. Operation data: time and type of surgery, duration of surgery, antimicrobial prophylaxis (antibiotic, dose, time of application), additional interventions, wound contamination class according to the CDC, exclusion criteria, side effects during application of product.
4. Laboratory values such as hemoglobin, leukocytes, creatinine, CRP.
1. They are recorded using the hospital medical records of the patients during hospitalization.

9.3.2 Post-discharge follow-up (FU1 and FU2)

The post-discharge follow-up is performed by IP nurses on day 30 (-50) (FU1) and for patients in cardiac surgery on day 365 (-week 56) (FU2) through standardized phone interviews with the patients. At least five telephone attempts must be documented before a patient can be considered as lost-to-follow-up. Six questions are asked about unplanned medical visits, re-hospitalization, antibiotic prescription, and clinical symptoms of infection. Any suspected or unclear case triggers further contacts with the family or hospital physician to gather any available additional information. Data recorded includes: time of follow-up, status of patient, deceased (yes/no), reoperation (SSI/non-infectious complications), rehospitalization for SSI, SSI present, depth of SSI, time of diagnosis, microbiology results and if present responsible microorganism.

10. SAFETY

10.1 Drug studies

Not applicable.

10.1.1 Reporting of serious side effects (SAE) and other safety related events

Reporting of SAEs

Not applicable.

10.1.2 Follow-up of (serious) adverse events

Not applicable.

10.2 Medical Device Category C studies

Not applicable.

10.3 Medical Device Category A studies

Not applicable.

11. STATISTICAL METHODS

11.1 Hypothesis

We hypothesize that neither compound is inferior to the other in terms of primary outcome SSIs. We define non-inferiority as crude rate of SSIs not exceeding plus/minus 2.5% in cardiac surgery and abdominal surgery combined (7.5% ± 2.5%) based on surveillance data of Swissnoso.

11.2 Determination of Sample Size

Based on a review of Swissnoso SSI rates, we estimate the crude SSI rate in cardiac surgery to be 5% and in abdominal surgery to be 10%, adding up to an overall crude SSI rate of 7.5%, assuming equal proportions of the respective surgery types. We dimensioned the study to have 80% power at a significance level of 0.05 with an absolute non-inferiority margin of 2.5%. According to the sample-size calculation ("sealed envelope" website confirmed using R (package "TrialSize", function "TwoSampleProportion.NIS")) 1,374 patients are needed in each group. Assuming a maximum of 10% dropout from the trial, this would lead to a total sample size of 1,527 in each group, and 3,054 patients overall.

11.3 Statistical criteria of termination of trial

The trial will be terminated if either the calculated sample size is reached, or following the interim analysis one of the compounds is clearly superior as described in point 11.4.4.

11.4 Planned Analyses

11.4.1 Datasets to be analysed, analysis populations

The primary endpoint will be calculated according to intention to treat principles, i.e. all eligible patients randomized to treatment with at least one follow-up telephone interview (30 (-50) days for most surgeries, 30 (-50) days and 365 days (-week 56) for cardiac surgery).
Descriptive and univariable statistics are used to characterize the study participants and to compare the baseline characteristics of the two groups. Difference between patient characteristics will be determined with the use of the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables as well as for comparing rates of SSI.
The consistency of the effects of the study intervention on infections across different types of surgery will be examined with the use of an interaction test. To determine whether the results were consistent across the three participating hospitals, a prespecified Breslow–Day test for homogeneity will be performed. For continuous factors, we will use a single-variable logistic-regression model that involves generalized estimating equations (GEE) and mixed effects models to account for hospital site as a random effect. A multivariate logistic-regression analysis will be performed with variables deeming significant in univariate analyses ($P \leq 0.10$). We compare the primary outcome and other categorical outcomes between groups and calculate relative risks with 99% confidence intervals.
The analysis will be done during interim analysis after 12 months and upon termination of the trial.

11.4.2 Primary Analysis

The primary analysis model is a comparison of the SSI rates between the two groups. We will be using a standard chi-square test for this comparison, with statistical significance defined to be a p-value less than 0.05.

11.4.3 Secondary Analyses

As described in sections 5.2 and 11.4.1.

11.4.4 Interim analyses

The primary outcome SSI will be analyzed after 12 months and in case of a clear superiority of one of the compounds the study will be stopped, and the study sites will return to their regular disinfection compound.

11.4.5 Safety analysis

Not planned.

11.4.6 Deviation(s) from the original statistical plan

Deviations from the original statistical plan will be fully documented and submitted for approval by the appropriate committee.
Any extreme values will be investigated to determine if the patient differs significantly in any way from other patients.

11.5 Handling of missing data and drop-outs

Patients dropping out will be replaced until the required sample size in the appropriate group is reached. A complete case analysis will be performed on patients with complete baseline and follow-up measurements.
We do not envisage there being any covariate missingness at baseline, assuming that the information is collected for all eligible patients. However, multiple imputation (MI) will be used should there be missing covariate data.
Missing endpoint information is more likely to occur due to the relative unreliability of contacting individuals for a telephone interview. We will again use MI for investigate the potential effects of the missing endpoint information.
Missing at random (MAR) will be assumed throughout. However, if the missing data analysis reveals that this assumption appears less plausible, a sensitivity analysis will be performed.

12. QUALITY ASSURANCE AND CONTROL

12.1 Data handling and record keeping / archiving

An eCRF is provided by the SwissRDL of the Institute of Social and Preventive Medicine at the University of Berne which is password protected and saved on the MEMdoc central server. For each enrolled study participant the eCRF is maintained. ECRFs will be kept current to reflect subject status at each phase during the course of study. Participants will not be identified in the eCRFs by name or initials and birth date. Appropriate coded identification will be used. It is assured that any authorized person can be identified.
Additional data on allocation to group, study center and surgical subspecialty, side effects, exclusion criteria and clinical and laboratory data is entered in a separate eCRF also at the SwissRDL database. The same CRF number will be used. Only directly involved study personnel will be allowed to access this eCRF.

12.1.1 Specification of source documents

All data are directly recorded into the two eCRFs, which are considered the source documents.

12.1.2 Record keeping / archiving

All study data will be archived at the SwissRDL center in Berne. Data is stored for a minimum of 10 years after study termination. Study specific data (center, allocation, inclusion/ exclusion criteria, side effects, concomitant diseases not part of the Swissnoso-ANQ-SSI-Surveillance, laboratory values) will be deleted 10 years after termination of the study. Data recorded for the Swissnoso-ANQ-SSI-Surveillance as a quality project mandated by the federal government will be stored longer but not for scientific reasons.

12.2 Data management

Data will be entered by study personnel or IP nurses (follow-up) and validated manually by study personnel and electronically using range checks for data values. MEMDoc offers an internet-based support for data entry, query management, and monitoring. Various data validation rules automatically apply during data entry. Inventory reports are available for every hospital, signalling cases to be completed or with possible errors. The database will be run on a secure server at the SwissRDL center of the University of Berne.

12.2.1 Data Management System

Data is entered online in a pre-existing database provided by the SwissRDL of the Institute of Social and Preventive Medicine at the University of Berne which is password protected and saved on the MEMdoc central server. The database was programmed by the former MEM-Center of the University of Berne, which was now renamed to SwissRDL. This database has been in use for surveillance of SSI by Swissnoso and ANQ since 2009. Information technology specialists, a dedicated database manager, and a dedicated biostatistician are responsible for the database.

12.2.2 Data security, access and back-up

Open and non-codeddata is only available at the corresponding centers. Study nurses and infectious disease physicians responsible for the data collection at their centers will enter data online in the Swissnoso/ANQ database where data is coded. The database is password-protected. In case of necessary data cleaning the study team will provide the CRF number to the centers. Staff at the centers are the only ones to access open and noncoded data.
The complete module database is coded and backed up on the module every hour. Hourly backups are rotated daily, and daily backups are rotated monthly. Data is coded with an AES256 algorithm strong enough for classified information. The clinical data on the MEMdoc central server is coded

and backed up daily on two separate file systems. The Oracle database also maintains continually updated archive logs of each database transaction (mirrored in two locations). In the unlikely event of a failure, these logs can be used with the backups to revert the database to virtually any state. Any accidental disclosure of patient data is avoided by password protection and assignment of access on a personal level. All persons entering data are recorded therefore traceability of the data entries are assured.

12.2.3 Analysis and archiving

The MEMDoc database will be run and archived on a secure server at SwissRDL of the University of Berne.

12.2.4 Electronic and central data validation

Various data validation rules and range checks automatically apply during data entry. Inventory reports are available for every hospital, signalling cases to be completed or with possible errors. Data will be additionally validated manually.

12.3 Monitoring

The Sponsor-Investigator and a designated study monitor from the Clinical Trial Unit Basel will conduct three routine monitoring visits per site, done by the designated study monitor. The first visit approximately within four weeks after inclusion of the first patient in each center, the second visit approximately one year after the first monitoring visit at each center, as well as a third visit after inclusion of the last visit of the last patient in each center. The purpose of the visits is to confirm the following:

- Verify the qualifications of the local Investigators and inform the Investigators of responsibilities and the procedures for ensuring adequate and correct documentation.
- The study is being conducted according to the protocol and within the specified time frame.
- Presence without contradiction of general consent for patients.
- The data are being collected accurately and completely on eCRF and source documents.
- Adverse events are being correctly reported.
- The facilities and staff remain adequate.

The local Investigators ensure that source data and documents are made accessible to the study monitor and answer questions by the study monitor. Detailed description of monitoring activities will be defined in the study specific monitoring plan.

12.4 Audits and Inspections

The study documentation and the source data/documents are accessible to auditors/inspectors including CEC, and CA and questions will be answered during inspections. All involved parties must keep the participant data strictly confidential.
External audits regarding quality of data assessment will be performed by the regular auditory teams of Swissnoso every six months at all participating centers as described in point 6.1. They will have full access to source data. They have no access to study specific data.

12.5 Confidentiality, Data Protection

All documents and data shall be produced and maintained in such a way to assure control of documents and data to protect the subject's privacy. Direct access to the source documents will be permitted for the purposes of monitoring audits and inspections. The protocol will be made public online via the Forschungsdatenbank of the University of Basel, ClinicalTrials.gov and SNCTP prior to initiation of the trial. During the study statistical code and the dataset will only be accessible by

members of the study group and regulatory authorities. After the study other researchers will have the possibility to access the data in anonymized form after the primary evaluation of our study as described below (Point 13).

12.6 Storage of biological material and related health data

Not applicable.

13. PUBLICATION AND DISSEMINATION POLICY

The study results will be published in a peer-reviewed journal after final analysis. Results will also be presented as posters on international congresses. In addition, the results will be made available to the interested stakeholders via the website of Swissnoso free of charge by means of an editorial note in the Swissnoso Bulletin.
The study protocol will be made available online via the Forschungsdatenbank of the University of Basel, ClinicalTrials.gov and SNCTP.
Other researchers will have the possibility to access the data in anonymized form after the primary evaluation of our study. Researchers will have to submit a proposal to the scientific board of Swissnoso stating their intent and goals of the study and eventually access to the data will be granted. No financial reimbursements are necessary; Swissnoso will have to be mentioned in the acknowledgements of a putative publication.

14. FUNDING AND SUPPORT

14.1 Funding

The Swiss National Science Foundation assures a grant CHF 1,016,000 and provides herewith financial support for this investigator-driven study which covers the costs for the human and technical resources to conduct the study.

14.2 Other Support

Infrastructures of the participating centers may be used free of charge.

15. INSURANCE

Not applicable.

16. REFERENCES

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17. APPENDICES

17.1 CDC/NHSN criteria for SSI

“DEFINITIONS OF SSI: For surveillance classification purposes, SSIs are divided into incisional SSIs and organ/space SSIs. Incisional SSIs are further classified into those involving only the skin and subcutaneous tissue (called superficial incisional SSIs) and those involving deep soft tissues of the incision (called deep incisional SSIs [e.g., fascial and muscle layers]). Organ/space SSIs involve any part of the anatomy (e.g., organs or spaces), other than the incision, opened or manipulated during the operative procedure (Figure).”

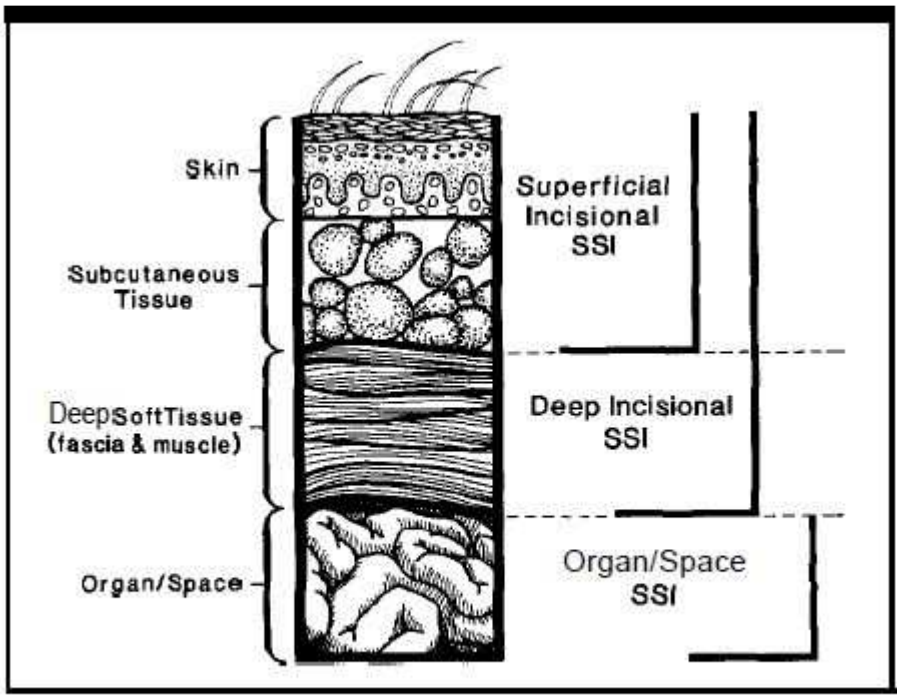

FIGURE. Schematic of SSI anatomy and appropriate classification.

Seperately provided documents

1. eCRF Swissnoso SSI Surveillance
2. eCRF study personnel PICASSo
3. Swissmedic Information Braunderm®, Softasept® Chlorhexidin Lös 2% gefärbt
4. Information on and general consent University Hospital of Basel (USB), University Hospital Zurich (USZ), Inselspital Bern
5. Information Swissnoso on SSI Surveillance
6. Swissnoso data regulations
7. Swissnoso criteria for diagnosis of SSI
8. Variable list application CleanCareMonitor
9. CV Prof. Dr. A. Widmer, PD Dr. J. Marschall, PD Dr. S. Kuster
10. GCP proof Prof. Dr. A. Widmer
11. Draft of study agreement USZ and Inselspital Bern
12. Decree of funding by SNSF

13. Swissnoso guide for SSI Surveillance