Published in final edited form as:

Arch Orthop Trauma Surg. 2020 June ; 140(6): 741–749. doi:10.1007/s00402-019-03303-7.

Development and challenges in setting up an international bone infection registry

Stephen L. Kates¹, Severine Hurni², Maio S. Chen²

¹Department of Orthopaedic Surgery, Virginia Commonwealth University, 1200 East Broad St, PO Box 980153, Richmond, VA 23298, USA ²AO Clinical Investigation and Documentation, Davos, Switzerland

Abstract

Introduction—Osteomyelitis is an increasing burden on the society especially due to the emergence of multiple drug-resistant organisms. The lack of a central registry that prospectively collects data on patient risk factors, laboratory test results, treatment modalities, serological analysis results, and outcomes has hampered the research effort that could have improved and provided guidelines for treatments of bone infections. The current manuscript describes the lessons learned in setting up a multi-continent registry.

Materials and methods—This multicenter, international registry was conducted to prospectively collect essential patient, clinical, and surgical data with a 1-year follow-up period. Patients 18 years or older with confirmed *S. aureus* long bone infection through fracture fixation or arthroplasty who consented to participate in the study were included. The outcomes using the Short Form 36 Health Survey Questionnaire (version 2), Parker Mobility Score, and Katz Index of Independence in Activities of Daily Living were assessed at baseline and at 1 month, 6 months, and 12 months. Serological samples were collected at follow-ups.

Stephen L. Kates, Stephen.Kates@vcuhealth.org.

Conflict of interest Stephen Kates has received multiple research grants from both governmental (NIH and AHRQ) and private sources (AO Foundation and PCORI). Severine Hurni and Maio Chen declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The ethics committees (reference number) consulted were: Region-shuset, Viborg, Denmark (#1-10-72-18-13), Ethic Commission at Hospital Italiano, Buenos Aires, Argentina (#2288), Ethic Commission beider Basel, Switzerland (#EK 353/12), Conjoint Health Research Ethics Board, University of Calgary, Canada (#REB13-0179), Ethics Committee of the First Affiliated Hospital of Third Military Medical University, Chongqing, China (#Keyang-2014(8)), University of Missouri–Columbia Health Sciences Institutional Review Board, USA (#1205478), Geisinger Institutional Review Board, Danville, Pennsylvania, USA (#2014-0313), Ethics Committee University Giessen, Germany (#94/13), Zunyi Medical University Ethics Committee (no reference number), Ethics Committee of Zhejiang Provincial People's Hospital, China (#2013KY064), Ethics Committee of the Hamawaki Orthopedics Hospital, Hiroshima, Japan (no reference number), Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster, Hong Kong (#UW 13-179), Ethics Committee of the Medical University Innsbruck, Austria (#UN4927), Medical Ethics Commission UZ KU Leuven/Onderzoek, Leuven, Belgium (#S57451), Ethik-Kommission der Bayerischen Landesärztekammer, Munich, Germany (#12121), Ethics Commission, University Regensburg, Regensburg, Germany (#14-102-0321), Virginia Commonwealth University IRB Panel, Richmond, VA, USA (#HM20006017), Unity Health System IRB, Rochester, NY, USA (#419), and University of Rochester Research Subjects Review Board (RSRB00043910).

Informed consent Informed consent was obtained from all individual participants included in the study.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Results—Contract negotiation with a large number of study sites was difficult; obtaining ethics approvals were time-consuming but straightforward. The initial patient recruitment was slow, leading to a reduction of target patient number from 400 to 300 and extension of enrollment period. Finally, 292 eligible patients were recruited by 18 study sites (in 10 countries of 4 continents, Asia, North and South America, and Central Europe). Logistical and language barriers were overcome by employing courier service and local monitoring personnel.

Conclusions—Multicenter registry is useful for collecting a large number of cases for analysis. A well-defined data collection practice is important for data quality but challenging to coordinate with the large number of study sites.

Keywords

Staphylococcus aureus; Bone infection registry; Implant-related infection; Registry development; Prosthetic joint infection; Fracture-related infection

Introduction

Osteomyelitis remains a serious problem in orthopedic and trauma surgery, causing increased length of hospital stay, cost of care, morbidity, and death rate [1–4]. An increasing burden of osteomyelitis was shown by a recent study based on a US population, confirming the impression of an increased annual incidence of osteomyelitis between 1969 and 2009: The overall annual incidence increased from 11.4 cases per 100,000 person-years between 1969 and 1979 to 24.4 per 100,000 person-years between 2000 and 2009 [4]. Although this study was probably the first of its kind to describe the burden of osteomyelitis on a general population and that it identified *Staphylococcus aureus* (*S. aureus*) being the most frequent causal organism of osteomyelitis, no information was available on the proportions of methicillin-resistant *Staphylococcus aureus* (MRSA) infections over time. Given the rise in antibiotic-resistant microorganisms, this gap in knowledge is most regrettable for the purpose of surveillance and research.

Staphylococcus aureus has been identified as the most frequent pathogen isolated in various musculoskeletal infections [2, 5–8]. The emergence of MRSA strains and other multiple drug-resistant organisms further compounded the problem and reduced the success rates following treatment of infections [6, 9, 10]. Preoperative prophylactic measures such as prophylactic antibiotics and decolonization protocol have been advocated in combating MRSA [8, 11]. The success of these measures, however, has been controversial and calls into question their cost-effectiveness and raised concerns of good antibiotic stewardship [12, 13].

The complex interaction between the human immune system and *S. aureus* remains poorly understood and challenging to study. Although there have been national surveillance programs, for example, a US governmental program that collected information on hospitalization for infections involving the extremities [1] or the German OP-KISS that collects and analyzes surgical site infections following certain procedures [14], they do not collect laboratory data or analyze patients' immune response to bone infections. The lack of centralized registries in bone infection has hampered the research effort that could have

improved and provided guidelines for treatments. A central registry would enable hospital wards and clinics to prospectively collect data from individual cases with a consistent method in an organized manner. Such standardization would take the most important influences and risk factors into account and thus make construction of prognostic models possible.

To gain a more global understanding of the complex picture of bony infection caused by *S. aureus*, we established an international multicenter registry on bone infection. We collected patient data, laboratory test results, treatments, outcomes, and serological samples. This should allow us to study the influence of demography, comorbidity, treatment modality, immune response, and microbiology of *S. aureus* on clinical outcomes and quality of life in better detail. This manuscript describes the challenges of establishing such a pilot registry and measures taken to overcome the barriers with the hope that we can assist other investigators in establishing similar registries in the future. Detailed outcomes will be presented in subsequent papers.

Patients and methods

Setting

The current registry was a prospective observational case series of patients with long bone *S. aureus* infection. Aside from the baseline assessments, patients were followed up at 1 month, 6 months, and 12 months.

It was planned to include 20 investigational sites. Site selection should take into consideration the caseload, geographical location, and the settings to assure a balanced (demographically and socioeconomically) and diverse patient population. Sites were selected through personal and academic contact by the principal coordinating investigator (PCI).

Site recruitment and ethics approval

Contracts were negotiated between the PCI's home institute and the investigational sites. The applications for ethics approval were submitted by individual investigational sites with the assistance of a central clinical research organization (CRO) to the responsible institutional review boards (IRB) or ethics committee (EC).

Study and data management

The study was conducted according to the ISO 9001 guidelines and registered at [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01677000) (no. NCT01677000). Data management and data handling and protection were conducted according to the guidelines of ISO 14155 and ICH GCP and applicable regulations. The central CRO monitored the study and the site staff entered all data into a web-based electronic data capture system, REDCap [15].

Site initiation visits, monitoring visits, and close-out visits in North America, Europe, Hong Kong, and Japan were performed exclusively by the personnel from the CRO. In South America and China, however, these were performed mainly by local clinical research associates (CRAs) trained by the CRO.

All sites received a detailed study protocol and the personnel were trained on the proper study procedures. All appropriate study materials including instructions (in form of a manual and a training video) for sample collection and handling (see below) were prepared by the PCI and the CRO.

Study-related questions were answered mainly by the CRO and occasionally by the PCI. A “frequently asked question” document was developed in English to ensure that consistent answers were given. Regular communication via newsletters was designed to update sites of the status of the registry and to motivate site personnel.

Language barrier

It was envisioned that multiple countries worldwide should take part in the registry. Although contracts were always done in English, documents such as the informed consent form (ICF) and patient questionnaires must be submitted to the ethics authorities in local languages; these were translated through the collaboration of the CRO, local site principal investigators (PIs), and professional translators. Validated SF-36 version 2 (v2) questionnaires in various languages were readily available and did not require custom translation. The study protocol was translated into Spanish and Chinese via the same process.

Sample collection and transport

The registry planned the collection of patient infection samples, i.e., blood, nasal swabs, and wound swabs, for the confirmation of infection organisms and the investigation of the level of host humoral response to the infection. Aside from the previously mentioned instructions (a manual and a training video) to ensure a uniform sample collection and handling, standardized sample collection kits were shipped from the central laboratory in the US to all investigational sites along with return shipping labels. Commercial courier service was engaged for specimen transport to the central laboratory in the US and in China.

Patient population

The inclusion criteria were patients aged 18 years or older with confirmed *S. aureus* infection (either methicillin resistant or sensitive). The infection must involve a long bone (i.e., femur, tibia, fibula, humerus, radius, ulna, and clavicle) due to fracture fixation or arthroplasty. *S. aureus* infection could be confirmed by positive culture from baseline examination or a prior definitive diagnosis of ongoing *S. aureus* infection at the same surgical site by the treating surgeon.

Patients must be judged to have the capability to understand the content of the patient information and the patient ICF and sign the written informed consent to participate in the study.

Endpoints

Patient attributes, infection history, and comorbidity (Charlson comorbidity index) [16] were recorded at the baseline visit. Medical and surgical approach (including implants used), hospitalization (administrative details, length of stay, and rehospitalization), and revision

surgeries were captured. Blood laboratory parameters were assessed by local laboratories at baseline and at 6 and 12 months. Blood samples (plus nasal and wound swabs collected at baseline) were also drawn and processed at baseline, 6 and 12 months for further processing and shipment to central laboratory for microbiologic/serologic analyses.

The 36-Item Short Form Health Survey (SF-36), v2 [17], Parker Mobility Score (PMS) [18], and Katz Index of Independence in Activities of Daily Living (Katz ADL) [19, 20] questionnaires were to be filled out at baseline, 6 months, and 12 months. Individual infection healing status was assessed at all FU time points by individual investigational sites.

Complications from registry-specific procedures, i.e., additional blood draws and nasal swabbing, were recorded. In-hospital complications and adverse events that led to hospitalization or prolonged hospitalization were documented for safety analysis.

Amendment of study protocol

It was originally envisioned to include 400 patients (roughly 20 patients per site) in the registry, and to exclude patients with mixed infections (i.e., infections with additional organisms on top of *S. aureus*). Due to slow enrollment (Fig. 1a), 2 years into the registry, an interim power analysis was performed for mortality and the patient number was reduced to 300. Patients with *S. aureus* mixed infections were also included, assuming they otherwise fulfilled the inclusion criteria.

With a patient number of 300, it was the intention that a prognostic model shall be created. Assuming an event incidence (e.g., recurrence of infection) of at least 30 per 100, 90 events could be expected from the current registry, which would be sufficient to accommodate a prognostic model with up to 9 variables.

Results

Site recruitment and ethics approval

Contracts were successfully negotiated and signed with 21 investigational sites from 10 countries located in 4 continents (Asia, North and South America, and Central Europe). All participating investigational sites were university-affiliated or university hospitals. Due to legal disagreements, costs, and payment issues, the contract negotiation was delayed in several sites. Eventually, either the site had a delayed start in enrollment, dropped out at early stage after ethical approval, or never recruited any patients. On average, contract negotiation took 6–12 months per site and in one extreme case, 3 years.

In contrast to contract negotiation, the application for ethics approval was relatively smooth and all sites intending on joining the registry made serious efforts to obtain ethics approval. No sites dropped out because of failure to obtain IRB/ethics approval. However, ethics approval was at times a lengthy procedure and it took on average 3–6 months.

The PIs from one European and one Asian site moved during the registry resulting in the stopping of patient recruitment at those sites, although patient follow-ups did carry on for the rest of the registry period. In addition, the relocation of the PCI at year 4 of the registry

caused additional loss of time due to contract re-negotiation and temporary slow patient recruitment.

Patient recruitment and dropouts

The first written informed consent was signed on November 2, 2012 and the last, August 13, 2017. As mentioned in the methods section, the initial patient recruitment was slower than the original projection (Fig. 1a). Even with the reduction of patient number, a two-and-a-half years extension was necessary to reach the recruitment goal, with 362 patients signing the ICF (Fig. 1b). After the exclusion of ineligible patients who either did not commence treatment or did not have infection with *S. aureus* in a long bone, the resulting full analysis population was 292 patients (Fig. 2). The success of patient recruitment differed drastically among different sites, ranging from 2 to 67 patients in the full analysis population. In addition, only five sites reached the target of 20 patients. It should also be mentioned that only three patients were recruited in the continent of South America—a patient population not representative of the continent.

Although patient dropout is typical in clinical trials, this registry recorded a relatively high dropout number of 82 patients (28.1%) (full analysis population), not including the 14 patients (4.8%) who died. Aside from loss of follow-ups, reasons frequently cited for drop out included the patient was too ill, lived too far away, and lack of transportation (Table 1).

Language and cross-cultural barrier

To secure the participation of Asian sites, several personal trips by the PCI were required to secure the commitment of the sites and to smooth out logistical issues—some with great success and some with disappointing results. Due to the Chinese regulation that prohibited exporting of human materials from China (excluding Hong Kong), a second central laboratory had to be established to manage and analyze the Chinese specimens in China.

Aside from translating certain documents into the local languages, the language barrier was overcome largely by engaging local CRAs: two CRAs located in Hong Kong and one CRA located in Peru were enlisted to perform some of the site initiation, monitoring, and/or site close-out visits.

Sample collection and transport

Sample collections were done properly at nearly all sites. The site investigators utilized the sample collection kits and in nearly every case, specimens were properly processed and stored in -80°C freezers before the transport. One exception was the freezing of blood samples without first centrifuging them leading to hemolyzed blood samples at one site. Another glitch was the shipping of sample collection kits near expiration dates, these then had to be discarded leading to the disposal of a small number of samples.

Using professional courier companies, sample transportation to the central laboratories was largely uneventful. The courier service companies were charged with and performed properly the replenishment of dry ice during shipping. In total, only three specimens were lost in transit with unknown cause.

Endpoints

The compliance rates of sampling and questionnaire completion at baseline were high, between 95 and 100%. Except for the blood sample collection for local laboratory tests, the missing rates ranged between 5 and 13% at 6 and 12 months (Table 2).

Discussion

The current registry aimed to include a large number of investigational sites around the world so as to achieve a better understanding of the global long bone infection trends and epidemiology. Due to the large number of sites for relatively small number of patients per site, the resource requirement for monitoring was especially intense. Not only the total number of monitoring trips was higher than usual, inconsistency in practice was more likely to happen. For example, the timing of written consent varied at different sites: some sites had the patients sign the ICF before the positive culture results were available, whereas others had the patients sign the informed consent only after *S. aureus* infection was confirmed. Further, although the study protocol specified that blood samples should be taken for local laboratory tests at baseline, 6 months, and 12 months, the blood sampling missing rates were high at 6 and 12 months. We suspect that some sites followed their standard of care procedure, which did not include laboratory blood work at 6 and 12 months.

The global nature of this registry added another level of complexity to the study. Aside from the usual challenges of conducting clinical research, contract negotiation, ethics submission, unifying data assessment and sample handling, the logistics of shipping study materials (including biological specimens), and language and cultural barrier all required careful planning, patience, and persistence—not to mention a realistic budgeting (we estimated that the overall cost was approximately \$10,600 per patient successfully included in the study). The hiring of local CRAs, a clear and precise manual and training video for sample handling, a “frequently asked questions”, and standardized sample collection kits were extremely helpful in harmonizing practices of different sites. In our case, the courier service was quite reliable and contributed to the successful collection of infection samples for eventual analyses.

As usual, site selection was a crucial step to the success of this registry. Even with careful feasibility check before sites were recruited to the registry, some sites turned out to have very low caseload. Specialist hospitals that routinely dealt with complications from a large catchment area proved to be the most productive in terms of the number of cases recruited. On the other hand, a significant challenge to the development of this infection registry proved to be investigator engagement.

The nature of infections caused certain special challenges in a registry. For example, since patients were supposed to have confirmed infection, by the time the patients reached our investigational sites, many of them had had prior infection-related treatments. This created difficulty in standardizing baseline/FU timing, since the patients were at different stages of infection/recovery. Such heterogeneity posed difficulty in designing meaningful analyses. Another example was the lack of a uniform definition of healing status; the result was that each site assessed the healing status based on its own definition—or the lack of it.

Finally, as a multi-continental registry, special care had to be taken to ensure that all questions were well thought out and unambiguous to obtain clean data. One hard lesson learned concerned the question of the number of surgeries was that some sites entered planned multistage surgeries as one surgery, while others entered these as multiple surgeries.

In summary, the results of the current registry identified many potential pitfalls of a registry involving multiple study sites emphasizing the importance of site selection. Table 3 summarizes the problems encountered and some potential solutions. To ensure the external validity of the registry and to recruit enough patients, we strove to include a large number of study sites representing different parts of the world. Throughout the study, an enormous amount of administrative effort was requirement for contract negotiation, IRB/ethics approval and application, study management, and standardizing study procedures. Although the goal to include a large number of study sites was achieved, some sites recruited very few patients. As a result, the registry should have focused on the high performing sites earlier and similar geographical coverage and number of patients enrolled could have been achieved. This smaller number of study sites could have allowed better harmonization of the enrollment process, closer monitoring of enrollment performance, and timely corrective actions for data entry and specimen collection problems.

Strengths

Due to the multicenter and multi-continent nature of the current registry, a description of regional practices, causal pathogens, and outcomes should be possible. The collection of serum and tissue samples will also allow the analyses of host humoral responses providing a better picture of *S. aureus* infection.

Limitations

The original intention of the registry was to include sites from around the globe. In the end, patients were recruited mainly from North America, Central Europe, and China (representing Asia)—this does not include all regions of the world. In addition, due to the uneven distribution of the number of patients, comparing results by sites may not be possible.

As this registry was intended to be a pilot study, the number of patients was small and the follow-up period was short (1 year) for deep infection. Nevertheless, we hoped to capture some of the obvious trends and provide some initial indications of a prognostic model for outcomes.

Acknowledgements

The authors wish to thank Philip Buescher for his help and support with conduct of this study. We also wish to thank the numerous study coordinators, research associates and other study personnel, and the medical statisticians for their dedication and expertise. Last but not least, we would like to thank the study site principal investigators Drs Kjeld Søballe, Jorge Barla, Dirk Schaefer, Richard Buckley, Zhao Xie, James Stannard, Michael Suk, Volker Alt, Yi Liu, Bi Qing, Kiminori Yukata, Frankie Leung, Michael Blauth, Willem-Jan Metsemakers, Christoph Erichsen, Mario Morgenstern, Michael Nerlich, and Irvin Oh, who made this very complex project possible.

Funding This study was funded by the AO Foundation via the AOTrauma clinical priority program “Bone Infection”. Clinical Translational Science Award CTSA:Grant # 1UL1TR002649

References

1. Rubin RJ, Harrington CA, Poon A, Dietrich K, Greene JA, Moiduddin A (1999) The economic impact of *Staphylococcus aureus* infection in New York City hospitals. *Emerg Infect Dis* 5(1):9–17. 10.3201/eid0501.990102 [PubMed: 10081667]
2. Calhoun JH, Manring MM, Shirtliff M (2009) Osteomyelitis of the long bones. *Semin Plast Surg* 23(2):59–72. 10.1055/s-0029-1214158 [PubMed: 20567728]
3. Anderson DJ, Arduino JM, Reed SD, Sexton DJ, Kaye KS, Grussemeyer CA, Peter SA, Hardy C, Choi YI, Friedman JY, Fowler VG Jr (2010) Variation in the type and frequency of postoperative invasive *Staphylococcus aureus* infections according to type of surgical procedure. *Infect Control Hosp Epidemiol* 31(7):701–709. 10.1086/653205 [PubMed: 20518637]
4. Kremers HM, Nwojo ME, Ransom JE, Wood-Wentz CM, Melton LJ 3rd, Huddleston PM 3rd (2015) Trends in the epidemiology of osteomyelitis: a population-based study, 1969 to 2009. *J Bone Joint Surg Am* 97(10):837–845. 10.2106/jbjs.N.01350 [PubMed: 25995495]
5. Foster TJ (2005) Immune evasion by staphylococci. *Nat Rev Microbiol* 3(12):948–958. 10.1038/nrmicro1289 [PubMed: 16322743]
6. Anderson DJ, Kaye KS, Chen LF, Schmader KE, Choi Y, Sloane R, Sexton DJ (2009) Clinical and financial outcomes due to methicillin resistant *Staphylococcus aureus* surgical site infection: a multi-center matched outcomes study. *PLoS ONE* 4(12):e8305 10.1371/journal.pone.0008305
7. Murillo O, Grau I, Lora-Tamayo J, Junyent J, Ribera A, Tubau F, Ariza J, Pallares R (2015) The changing epidemiology of bacteraemic osteoarticular infections in the early 21st century. *Clin Microbiol Infect* 21(3):254–258. 10.1016/j.cmi.2014.09.007 [PubMed: 25618436]
8. Perry KI, Hanssen AD (2017) Orthopaedic infection: prevention and diagnosis. *J Am Acad Orthop Surg* 25(Suppl 1):S4–S6. 10.5435/jaaos-d-16-00634 [PubMed: 27984341]
9. Chambers HF, Deleo FR (2009) Waves of resistance: *Staphylococcus aureus* in the antibiotic era. *Nat Rev Microbiol* 7(9):629–641. 10.1038/nrmicro2200 [PubMed: 19680247]
10. Planet PJ (2017) Life After USA300: the rise and fall of a super-bug. *J Infect Dis* 215 (suppl_1):S71–s77. 10.1093/infdis/jiw444 [PubMed: 28375517]
11. Humphreys H, Becker K, Dohmen PM, Petrosillo N, Spencer M, van Rijen M, Fordos A, Pujol M, Dubouix A, Garau J (2016) *Staphylococcus aureus* and surgical site infections: benefits of screening and decolonization before surgery. *J Hosp Infect* 94(3):295–304. 10.1016/j.jhin.2016.06.011 [PubMed: 27424948]
12. Reveles KR, Duhon BM, Moore RJ, Hand EO, Howell CK (2016) Epidemiology of methicillin-resistant *Staphylococcus aureus* diabetic foot infections in a large academic hospital: implications for antimicrobial stewardship. *PLoS ONE* 11(8):e0161658 10.1371/journal.pone.0161658
13. Banerjee S, Argaez C (2017) CADTH rapid response reports In: Topical antibiotics for infection prevention: a review of the clinical effectiveness and guidelines. Canadian Agency for Drugs and Technologies in Health Copyright (c) 2017 Canadian Agency for Drugs and Technologies in Health, Ottawa (ON)
14. Meyer E, Schroder C, Gastmeier P, Geffers C (2014) The reduction of nosocomial MRSA infection in Germany: an analysis of data from the Hospital Infection Surveillance System (KISS) between 2007 and 2012. *Dtsch Arztebl Int* 111(19):331–336. 10.3238/arztebl.2014.0331 [PubMed: 24875457]
15. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG (2009) Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 42(2):377–381. 10.1016/j.jbi.2008.08.010 [PubMed: 18929686]
16. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V (2011) Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *AmJ Epidemiol* 173(6):676–682 [PubMed: 21330339]

17. Ware JE Jr, Kosinski M, Dewey JE (2001) How to score-version 2 of the SF-36 Health Survey (Standard & Acute Forms), 3rd edn QualityMetric Incorporated, Lincoln, p 02865
18. Parker MJ, Palmer CR (1993) A new mobility score for predicting mortality after hip fracture. *J Bone Joint Surg Br* 75(5):797–798 [PubMed: 8376443]
19. Katz S, Downs TD, Cash HR, Grotz RC (1970) Progress in development of the index of ADL. *Gerontologist* 10(1):20–30 [PubMed: 5420677]
20. Katz S (1983) Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. *J Am GeriatrSoc* 31(12):721–727

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig. 1.

a Graph taken from study newsletter from 2015 showing the deviation of the number of patients consented from the original projection. **b** Patient recruitment after amendments

Fig. 2.
Patient recruitment by site

Table 1

Patient dropouts and deaths (full analysis population)

Study site	E1	E2	E3	E4	E5	E6	E7	A1	A2	A3	A4	A5	SA	NA1	NA2	NA3	NA4	NA5	Total
Number of patients	13	17	16	6	18	67	10	28	24	2	3	5	3	9	18	6	24	23	292
Number of deaths	1	2	1	1	2	2		1								1	2	3	14
Number of dropouts	1	1	9	0	1	21	0	3	8	2	0	1	0	6	10	1	9	9	82
Main reason for dropouts																			
Patient withdrew consent	1	3		1	1	1									1	1		2	10
Other																			
Physical hindrance ^a	1		1			1								2			2		7
Patient excluded by site ^b														2					2
Treatment successful															1				1
Lost to follow-up			5			19		3	8	2		1		2	8		7	7	62

*E*Europe, *A* Asia, *SA* South America, *NA* North America^aPatient was too ill, lived too far, had no means of transportation, started a new job, insurance would not pay^bReasons unknown

Table 2

Follow-up visits completion status and rates (full analysis population)

Assessment	Visit	N = 292			
		Visit status			
		Done	Missing	Dropout	Death
Visit	Baseline	292 (100%)	0 (0%)	0 (0%)	0 (0%)
	1 month	265 (91%)	15 (5%)	10 (3%)	2 (1%)
	6 months	216 (74%)	17 (6%)	49 (17%)	10 (3%)
	12 months	196 (67%)	0 (0%)	82 (28%)	14 (5%)
SF-36 completion	Baseline	281 (96%)	11 (4%)	0 (0%)	0 (0%)
	1 month	258 (88%)	22 (8%)	10 (3%)	2 (1%)
	6 months	212 (73%)	21 (7%)	49 (17%)	10 (3%)
	12 months	192 (66%)	4 (1%)	82 (28%)	14 (5%)
Blood samples taken	Baseline	292 (100%)	0 (0%)	0 (0%)	0 (0%)
	6 months	129 (44%)	104 (36%)	49 (17%)	10 (3%)
	12 months	109 (37%)	87 (30%)	82 (28%)	14 (5%)
Nasal swab taken	Baseline	292 (100%)	0 (0%)	0 (0%)	0 (0%)
	6 months	33 (11%)	N/A	49 (17%)	10 (3%)
	12 months	26 (9%)	N/A	82 (28%)	14 (5%)
Serum sample taken	Baseline	290 (99%)	2 (1%)	0 (0%)	0 (0%)
	6 months	194 (66%)	39 (13%)	49 (17%)	10 (3%)
	12 months	169 (58%)	27 (9%)	82 (28%)	14 (5%)
Wound swab taken	Baseline	276 (95%)	16 (5%)	0 (0%)	0 (0%)
	6 months	4 (1%)	N/A	49 (17%)	10 (3%)
	12 months	2 (1%)	N/A	82 (28%)	14 (5%)
EDTA sample taken	Baseline	288 (99%)	4 (1%)	0 (0%)	0 (0%)
	6 months	136 (47%)	N/A	49 (17%)	10 (3%)
	12 months	114 (39%)	N/A	82 (28%)	14 (5%)

N/A not applicable (not required by the study protocol for this FU)

Table 3**Problems encountered and suggested potential solutions**

Problems encountered	Potential solutions
Administrative difficulty and resource requirements in contract negotiation, IRB/ethics approval application, and site personnel training	Beware of local legal environment for contracting during site selection Realistic planning of study schedule Timely assessment of progress or lack of progress Minimize the number of sites to increase the general efficiency
Slow patient recruitment	Careful site selection Timely closure of underperforming sites Practical inclusion/exclusion criteria Realistic enrollment targets
Inconsistency in patient enrollment, enrolling ineligible patients, high blood sample missing rate, etc	Standardizing investigator training, e.g., using instruments such as training manual and video, answers to “frequently asked questions”, and standardized sample collection kits Close monitoring of enrollment process and early implementation of corrective measures Careful principal investigator selection
High dropout rate	No clear solution; close monitoring of the situation and striving for high engagement of the study sites (e.g., through newsletters, investigator meetings, site visits)
Heterogeneity of patient population and treatments limiting meaningful analyses	Predefine the infection history and status Anticipate and better define treatment procedures and surgical stages Larger sample size to allow later stratification of patient population according to the predefined infection history and status
Biological sample collection and transport	Standardized sample handling kits Utilizing professional courier service
Language and cultural barrier	Engaging well-trained local monitors Choose outcome measures with validated translations Beware of local regulations