Dear reader

It is always a great pleasure to introduce the annual report of the Basel Institute for Clinical Epidemiology and Biostatistics (CEB). CEB is a thriving clinical research institute providing forefront research with a relative small team of very dedicated clinical epidemiologists and biostatisticians. The scientific output over the last decade and also in 2014 has been excellent. Under the lead of Professor Heiner C. Bucher CEB has been able to lance every year several research projects that result in high quality publications in high impact factor journals which get heavily cited and also attract the media.

This year's highlights are two methodologically oriented publications that underline the importance of the development and adherence to clinical research protocols. In an international collaboration researchers from CEB have revealed that one out of five investigator initiated trials conducted in Switzerland, Germany or Canada is prematurely terminated due to insufficient patient recruitment. More worrisome, results from early discontinued trials get less frequently published. This finding reveals a disturbing waste of resources in clinical academic medicine and raises also ethical concerns. In another study using the same data source investigators from CEB demonstrated that claims of therapeutic effects from subgroup analyses are disturbingly frequently ill specified in protocols and the following publications, raising fundamental concern about the credibility of any claimed subgroup effect. The consequences from this publication are clear: Journal editors and their reviewers should insist for concurrent access to study protocols and submitted manuscript to verify any claimed subgroup effect.

2014 has been a year of transformation for the foundation and the institute. CEB, an associated institute of the University of Basel has been founded in 2001 and has been funded since then by our foundation ‘Stiftung Institut für klinische Epidemiologie’. This chosen set-up has been very successful because it made a start-up like organisation of the institute necessary with a very professional financial and project management. The University of Basel established the chair of clinical epidemiology and the foundation provided the core funding and funding for the infrastructure. After 14 years of financial support the founders, santésuisse, the trustee of social health insurers in Switzerland and the Gottfried and Julia Bangerter-Rhyner-Foundation have ceased their financial contributions. The institute has been very successful in competing for projects and funding and now achieves funding close to 90%. However, this situation is not sustainable and an increase in core funding is indispensable to guarantee the further success of the institute. Therefore, the Board of Trustees of the Foundation has decided to actively look for donors and also to enlarge the Foundation’s board with new members who shall assist us in attracting fundings. I express my gratitude to Mrs. Melinda Friolet for her very generous contribution to the Foundation.

I would like to thank both founder organisations that have provided a great support for the institute over many years. I would also like to thank Professor Bucher for his continuous enthusiasm and leadership. It is very refreshing to see what an inspiring research environment he has generated which is the source of many astute ideas and exciting projects. CEB has an excellent administration and project management that would not have been possible without the energy and dedication of Sonja Achermann. I would like to thank the entire team of CEB for all the great work we have seen in 2014. It is always a delight and fun to have a get-together with all team members for a Christmas dinner or at the last summer excursion in Lucerne. I happened to meet young bright scientists making me confident that CEB’s brilliant output is going to continue.

Reto Guetg MD
President of the Board of Trustees
Foundation Institute for Clinical Epidemiology
OUR MISSION
The mission of CEB is to improve decision making in health care.
• We investigate whether new or established technologies in medicine provide benefit to patients.
• We develop and teach the methods of evidence-based medicine to improve the quality of clinical research and to examine the effectiveness of new technologies in the real world setting.
• We generate and appraise evidence of medical interventions for frequent and important conditions or health problems with the goal to improve patient outcomes.
Our goal is an evidence-based health care at the local, national and international level.

OUR STRATEGY
Translation of new knowledge from basic science into clinical medicine (‘bench-to-bedside’) is essential for medical innovation. CEB has an explicit focus on translational health research to investigate how patients gain timely access to new technologies with clinically relevant benefits that are safe and represent added value to health care systems.

We have broad experience in comparative effectiveness research and Health Technology Assessment (HTA). We evaluate whether new diagnostic and therapeutic interventions are safe and improve patient outcomes when used in the real world setting. We evaluate the cost-effectiveness and the impact of new technologies on the health system level. CEB seeks innovative solutions to improve patient outcomes. Methodological research is at the forefront of our activities to advance the generation of better evidence in clinical research. We conduct own applied research projects for common conditions mainly in infectious diseases and primary care using large observational databases and routinely collected data. We design and conduct large scale pragmatic trials to document whether interventions lead to better outcomes when applied in a real world setting.

OUR PRINCIPLES
Collaboration with excellent local, national and international academic partners is a key principle of CEB to generate and validate new evidence in patient care. Under the lead of CEB an interdisciplinary network of excellence for Comparative Effectiveness and Health Economic Research has been formed in 2014 with researchers from three faculties at the University of Basel. We provide high quality evidence for decision makers in health care, for clinicians, patients, health policy makers and buyers.

RESEARCH, CONSULTING, TEACHING
CEB is an associated institute of the University of Basel and combines excellence in research and teaching with an extensive consulting activity – a unique distinction from other academic institutions. Services offered range from consulting in clinical trial design to large scale observational and clinical trial data analysis, network, individual patient data and standard meta-analyses, Health Technology Assessments and methodological support for clinical researchers, governmental agencies, health insurers, and industry.
The team of CEB in the new office we will move to in 2015
RESEARCH HIGHLIGHTS OF CEB IN 2014

**Prevalence, characteristics, and publication of discontinued randomized trials.**
Kasenda, B. et al., *JAMA* 2014; 311(10): 1045-1051.

**Background:** Reasons for discontinuation of randomised clinical trials (RCTs) are insufficiently understood.

**Methods and results:** We investigated the prevalence, characteristics of discontinued RCTs and factors for nonpublication in archived protocols approved by 6 research ethics committees in Switzerland, Germany, and Canada between 2000 and 2003. After a median follow-up of 11.6 years, 253 of 1017 included RCTs were discontinued (24.9% [95% confidence interval (CI), 22.3%-27.6%]) but only 37.9% of discontinued RCTs (95% CI, 32.0%-44.3%) were reported to ethics committees. The most frequent reason for discontinuation was poor recruitment (101/1017; 9.9% [95% CI, 8.2%-12.0%]). Discontinued trials were more likely to remain unpublished than completed trials (55.1% vs 33.6%; odds ratio (OR), 3.19 [95% CI, 2.29-4.43]; P < .001).

**Conclusions and relevance:** Discontinuation of RCTs is common, with poor recruitment being the most frequently reported reason. Greater efforts are needed to ensure the reporting of trial discontinuation to research ethics committees and the publication of results of discontinued trials.

**Subgroup analyses in randomised controlled trials: cohort study on trial protocols and journal publications.**
Kasenda, B. et al., *BMJ* 2014; 349: g4539.

**Background:** Sub-group analyses are frequently reported in randomised controlled trials (RCTs), however, it remains often unclear to what extend sub-group analyses have been prespecified in trial protocols and are in agreement with corresponding full journal publications.

**Methods and results:** We analysed 894 protocols of RCTs from six research ethics committees in Switzerland, Germany, and Canada that were approved between 2000 und 2003 and identified 515 subsequent full journal publications. In total, 252 protocols (28.2%) included planned subgroup analyses. Of 515 identified journal publications, 246 (47.8%) reported at least one subgroup analysis, but only in 81 of 246 publications (32.9%), authors stated that subgroup analyses were prespecified, but this was not supported by 28 (34.6%) corresponding protocols. In 86 publications, authors claimed a subgroup effect, that was only in 36 (41.9%) instances prespecified in protocols.

**Conclusions and relevance:** Subgroup analyses are insufficiently described in the protocols of RCTs and over one third of sub-group analyses in publications are not documented in corresponding protocols. Definitive judgements regarding credibility of claimed subgroup effects are not possible without access to protocols and analysis plans of RCTs.

**Virologic and immunologic responses in treatment-naïve patients to ritonavir-boosted atazanavir or efavirenz with a common backbone.**

**Background:** Atazanavir boosted with ritonavir (ATV/r) and efavirenz (EFV) are both recommended as first-line therapies for HIV-infected patients. We compared the two therapies for virologic efficacy and immune recovery using real world data.

**Methods and results:** We included all treatment-naïve patients in the Swiss HIV Cohort Study starting therapy after May 2003 with either ATV/r or EFV and a backbone of tenofovir and either emtricitabine or lamivudine. We used Cox models to assess time to virologic failure and repeated measures models to assess the change in CD4 cell counts over time. All were fit as marginal structural models using both point of treatment and censoring weights. Intent-to-treat and various as-treated analyses were carried out: In the latter, patients were censored at their last recorded measurement if they changed therapy or if they were no longer adherent to therapy. Patients starting EFV (n = 1,097) and ATV/r (n = 384) were followed for a median of 35 and 37 months, respectively. During follow-up, 51% patients on EFV and 33% patients on ATV/r remained adherent and made no change to their first-line therapy. Although intent-to-treat analyses suggest virologic failure was more likely with ATV/r, there was no evidence for this disadvantage in patients who adhered to first-line therapy. Patients starting ATV/r had a greater increase in CD4 cell count during the first year of therapy, but this advantage disappeared after one year.

**Conclusions:** In this observational study, there was no good evidence of any intrinsic advantage for one therapy over the other, consistent with earlier clinical trials. Differences between therapies may arise in a clinical setting because of differences in adherence to therapy.
IMPACT OF RESEARCH FROM CEB

Our research gets frequently cited as reflected in the h-index of senior researchers (Table 1).

Table 1. h-Index of CEB’s senior researchers

<table>
<thead>
<tr>
<th>Senior Researcher</th>
<th>h-Index 1)</th>
<th>Standard value</th>
<th>Mean citation frequencies per publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD Dr. M. Briel</td>
<td>30</td>
<td>1.76</td>
<td>33.73</td>
</tr>
<tr>
<td>Prof. H.C. Bucher</td>
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<td>2.09</td>
<td>36.43</td>
</tr>
<tr>
<td>PD Dr. M.T. Koller</td>
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<td>1.54</td>
<td>16.98</td>
</tr>
<tr>
<td>Prof. A. Nordmann</td>
<td>14</td>
<td>0.87</td>
<td>61.52</td>
</tr>
</tbody>
</table>

1) The h-index allows to evaluate the performance of a single researcher and summarizes the publication and citation frequency in one figure. For example an h-index of 10 means that a researcher has published 10 publications that have been cited at least 10 times. By dividing the h-index by the number of years since the first publication a standard value may be derived. An h-index of over 20 with research experience of 10 years and over 40 with research experience of 20 years are generally considered as excellent.

The citation frequency of publications of senior staff from CEB is a further measure of the relevance of our research activity. The citation frequency of our publications constantly grew over the last 10 years.

Citations in Each Year

Figure 1. Citation frequency and number of indexed publications of senior researchers of CEB from 2004 to 2014 (Thompson Science Citation Index)
In 2014, CEB has published 40 publications in peer reviewed journals some of them in high ranked journals like JAMA, BMJ, European Heart Journal, Annals of Surgery and others. The large range of covered topics reflects our extensive collaboration with different partners, our methodological support for clinical research projects and our consulting activities. Publications of our methodological research deal with reasons for the premature discontinuation of clinical trials (publication 18), the consistency of planning and reporting of subgroup analyses in trial protocols and subsequent publications (19), an analysis on reasons for trial discontinuation in surgical trials (27) and an analysis on the quality of reporting of adverse events in surgical trials (28).

We have updated our systematic review in the Cochrane Library on the benefits of statins in acute coronary syndrome (32) and published a meta-analysis in complementary medicine on the blood pressure lowering effect of garlic preparations (26).

We compared the assessments of work ability for disability claims from a large multidisciplinary assessment center in Switzerland as estimated by claimants, treating physicians and assessment experts. Experts assessed claimant’s work ability higher than claimants and their treating physicians. The study reveals that a careful evaluation of the disability assessment process is needed to reduce disagreement between expert teams and treating physicians and to improve acceptance of the process. This study received high media attention in all major Swiss newspapers, national radio and TV stations.

Observational data analyses in HIV dealt with the effects of HIV-1 subtype and ethnicity on the rate of CD4 cell count decline in patients naïve to antiretroviral therapy (20) and investigated to what extend discontinuation of the antiretroviral drug tenofovir known to lower kidney function is reversible (39).
CEB TEACHING

CEB teaches principles of evidence-based medicine, critical appraisal skills, basics in clinical epidemiology and clinical research methodology to medical students in the bachelor and masters program at the University of Basel. Total teaching obligations in 2014 were 130 hours. Collaborators of the institute participate in post-graduate clinical investigator courses. Rachel Rosenthal and Benjamin Kasenda, PhD students of the interfaculty PhD program in epidemiology, successfully graduated in 2014. Publications from these PhD theses have been published in high impact factor journals like BMJ and Annals of Surgery.
CEB CONSULTING

Health Technology Assessment (HTA)
CEB initiated in 2014 a network of excellence for comparative effectiveness and health economic research involving researchers from the Faculty of Medicine, the Faculty of Business and Economics and the Faculty of Science at the University of Basel. CEB is the leader of a consortium commissioned in 2014 by the Swiss Medical Board for conducting HTA reports in Switzerland that involve partners from the network of excellence (ECPM Basel) and other Swiss universities (EBPI Zurich, ISPM Berne, iEH2 Geneva). We have finished the first report on operative versus conservative treatment of the acute and subacute lumbar radicular syndrome due to herniated lumbar disc. CEB had consultancy mandates from the Swiss Federal Office of Public Health that were related to Health Technology Assessment. CEB is also participating in work package 7 (Methodology development and evidence generation: guidelines and pilots production) of the European Network on Health Technology Assessment (EUnetHTA).

Clinical Methodological Research Consultancy Services
CEB is providing clinical epidemiological consultancy services to the Department of Surgery at the University Hospital Basel. Services include full methodological support and biostatistical data analyses. From this collaboration resulted 7 publications in 2014, 3 of them being methodological projects. For example, we analysed a larger cohort of patients with ischemic colitis, a condition with very unfavourable outcome and risk factors for in-hospital mortality in patients undergoing surgery (11).
Swiss Transplant Cohort Study

CEB was instrumental when the data centre of the Swiss Transplant Cohort Study (STCS) was founded in 2007. CEB is hosting the staff of this large multicentre cohort study which is collecting data on all solid organ transplantation in Switzerland. The study is funded by the Swiss National Science Foundation and the Swiss Ministry of Health. By the end of 2014 the study has included 3’310 transplanted solid organs and there are more than 70 projects approved by the Scientific Board of the STCS and 10 studies have been published (for details see www.stcs.ch). The goal of the STCS is to study transplantation related infections and tumors, genetics, immunology and psychosocial factors known to determine transplantation and patient outcome. The data centre is also responsible for establishing annual reports on transplantation outcomes to the Swiss Ministry of Health and for establishing organ specific and risk adjusted benchmarks for transplantation outcomes for the six transplantation centres in Switzerland.

My sincere thanks go to the entire staff and students of the institute. They have done a wonderful job and have been extremely productive. New ideas and projects have been developed. Senior scientists have been very successful in attracting projects and research grants. CEB is a very inspiring institute, and working with my team is a priviledge and also a lot of fun.

Prof. Heiner C. Bucher MD MPH
Director of the Institute
The mandate of CEB is to improve decision making in health care. Decision making in health care when caring for individual patients, at the population and system level always comprises uncertainty. Evidence from high quality research beyond any reasonable doubt is often limited in medicine because some diseases and events might be infrequent, data may be scarce and of limited quality or implications of certain decisions are unknown. Even in a situation where good evidence from experimental research of randomised controlled trials exists we often do not know if this evidence also applies when used in the real world setting in less selected patients who might differ from those included into clinical trials. We need better evidence for decision making because new efficacious and more expensive technologies are constantly entering the market and the demand for health care is growing but resources in health care are limited. CEB has developed innovative strategies and research programs to provide methodological input and empirical evidence that will improve better decision making in clinical care and at the health system level.

Research methodology
We conduct methodological research to improve the conduct and reporting of clinical trials and implementation research of innovative treatments. We are systematically collecting data of all innovative drugs with expedited and regular FDA approval between 2000 and 2015 and document the cumulative evidence on patient relevant treatment effects over time. We will systematically compare effects on patient-important outcomes from drugs frequently used without approval (off-label) and drugs used with approval (on-label) for the same indication. And we will develop a tool for monitoring in time implementation as well as economic and health related consequences of innovative treatments using real-world data on direct acting agents against hepatitis C.

Real world data
We have established a productive collaboration with the health insurer industry in Switzerland where for the first time, we will merge health resource use data with large observational cohort study data by anonymous probability linkage. This will allow us to address important questions on resource use and for economic modelling of innovative treatments in Switzerland in a pilot project of the Swiss HIV Cohort Study. We conduct large scale pragmatic trials in primary care in Switzerland and address important questions such as optimizing the use of antibiotics in primary care or the use of drugs in the elderly. We conduct large scale observational data analysis in HIV infection using advanced modelling techniques for confounder control to assess the comparative effectiveness of new treatments in the real world setting. We conduct meta-epidemiological studies to compare results from clinical trials conducted in an experimental setting and those from observational studies addressing the same research questions conducted in the real world setting. Results from this study will provide important insights under which circumstances results from observational data might provide reliable information on the effectiveness of interventions.

Health Technology Assessment
We have created a network of excellence for comparative effectiveness and health economic research at the University of Basel. This network will strengthen our capacities to provide Health Technology Assessments (HTA) for national and international organisations and address important health system questions. The network at the University of Basel provides a level of expertise in HTA, health system research, pharmacoepidemiology and health economics that is unique in Switzerland.

Consulting services
CEB is committed to providing high quality consulting services to national and international organisations and the pharmaceutical industry, which makes us unique in comparison with other academic institutions. Our interdisciplinary research, our link to clinical medicine – CEB serves as the clinical epidemiology unit of the University Hospital Basel – and our clinical epidemiologists who are also part time involved in clinical care are the strengths of our consulting activities making us an attractive partner.
Original Publications in peer reviewed journals


**Presentations**


Posters and Abstracts


ACCOMPLISHED PROJECTS IN 2014

HIV Infection, Swiss HIV Cohort Study ²

Predicting smoking cessation and its relapse in the Swiss HIV Cohort Study (SHCS)*
Smoking is highly prevalent among HIV-infected individuals and relatively few programmes have been established to help HIV-infected individuals to quit smoking. We will assess whether information from routine cardiovascular risk assessments can be used to predict those smokers that are most likely to quit smoking and in those who have quit the ones most likely to start smoking again.  
Start of project: 02.01.2011 - End of project: 30.06.2014

Virologic and immunologic responses to boosted atazanavir or efavirenz with a common backbone in treatment-naive HIV-infected patients. The Swiss HIV Cohort Study (SHCS)*
We will compare the efficacy of boosted atazanavir and efavirenz in the SHCS when used with preferred backbones tenofovir and emtricitabine or lamivudine. The study will mimic a recent randomised controlled trial where these two regimens had a similar rate of virologic failure but greater immune recovery under atazanavir to see if these trial results are achieved in clinical practice.  
Start of project: 01.04.2012 - End of project: 30.06.2014

Reversibility of estimated glomerular filtration rate in HIV-infected patients discontinuing tenofovir*
Tenofovir (TDF) is a commonly used antiretroviral drug for first-line treatment of HIV infection, but it has been shown to reduce estimated glomerular filtration rate (eGFR) and consequently increase the risk of chronic kidney disease. Few published studies have investigated the reversibility of eGFR following discontinuation of TDF give conflicting or inconclusive results. With the use of advanced modelling techniques we anticipate to generate more reliable estimates of eGFR change over time to assess the relative difference in kidney function between patients discontinuing a first therapy with TDF and those staying on the therapy.  

Cardiovascular and Lung Diseases

Predicting risk of serious outcome and death in patients with non-specific complaints: the BANC study±
Patients presenting to the emergency department (ED) with non-specific complaints (NSCs), such as weakness, challenge ED physicians since NSCs represent a broad spectrum of medical conditions. The objective of this study is to develop and validate prediction models for 30-day serious outcome and mortality in patients presenting to the ED with NSCs.  
Start of project: 01.02.2010 - End of project: 31.12.2014

Antiplatelet dual or monotherapy after transient ischemic attac or ischemic stroke? A meta-analysis of randomised controlled trials*
It is unclear whether early initiation of dual antiplatelet therapy after a stroke is better than antiplatelet monotherapy. In this meta-analysis of randomised controlled trials we evaluate the benefit and harms of dual antiplatelet therapy with aspirin and clopidogrel versus antiplatelet monotherapy initiated early after stroke or trans ischemic attack (TIA).  
Start of project: 01.06.2011 - End of project: 31.03.2014

² *Project Leadership ± Project Partner
Garlic for high blood pressure*
Some small studies report a blood pressure-lowering effect of garlic as compared to placebo. In this meta-analysis of randomised controlled trials comparing garlic to placebo or usual care we evaluate the effect of garlic on systolic and diastolic blood pressure in hypertensive patients.
Start of project: 01.01.2013 - End of project: 30.06.2014

Infectious Diseases

Corticosteroids versus placebo for patients with community acquired pneumonia (STEP trial):*
Early add-on therapy of corticosteroids for a limited time period may improve clinical outcomes in patients with severe infections. It is unclear whether this applies to patients with community acquired pneumonia (CAP). The objective of this randomised controlled trial is to compare a treatment with 7 days of corticosteroids with placebo in 800 patients with community-acquired pneumonia (CAP) with respect to time to clinical stability.

Effect of n-3 fatty acids on markers of brain injury and incidence of sepsis-associated delirium in septic patients:
Data regarding immunomodulatory effects of parenteral n-3 fatty acids in sepsis are conflicting. In this randomised controlled trial, we compared the effect of parenteral n-3 fatty acids on markers of brain injury, incidence of sepsis-associated delirium, and inflammatory mediators as opposed to standard treatment in 50 septic patients. The primary outcome was the difference in S-100β from baseline to peak level between both the intervention and the control group, compared by t-test. Changes of all markers over time were explored in both groups, fitting a generalized estimating equations model. We were unable to show an effect of n-3 fatty acids on markers of brain injury, incidence of sepsis-associated delirium, and inflammatory mediators in septic patients.
Start of project: 01.03.2010 - End of project: 28.02.2014

Pneumococcal vaccines for preventing pneumococcal infection - a systematic review:
In a first systematic review, we aim to examine the effects of pneumococcal vaccination on all-cause mortality, community acquired pneumonia, invasive pneumococcal disease and nasopharyngeal colonisation. The project is embedded in an economic modeling on pneumococcal vaccination in adults in Germany supported by the Robert-Koch-Institut in Berlin. In a second systematic review, we aim to examine the effects of pneumococcal conjugate vaccines on all-cause mortality, community-acquired pneumonia, invasive pneumococcal disease and acute otitis media in any population.
Start of project: 15.08.2013 - End of project: 31.03.2014

Health Technology Assessment

Reports for National and International Organisations

Deutsche S3 Leitlinie: Diagnostik, Therapie und Nachsorge der Patientin mit Zervixkarzinom:
We perform a series of systematic reviews for the S3-guideline on cervical cancer on behalf of the group lead by Prof. M.W. Beckmann, Leitlinienkoordination deutsche S3 Leitlinie, Universitätsklinikum Erlangen. In the first part of the project we prepared a cursory overview of the available evidence.
Start of project: 01.01.2013 - End of project: 31.01.2014
Methodological Research Projects

Epidemiology and publication of discontinued randomised trials, DISCO 1, main project:*  
When clinical research fails: a study of controlled trials that were discontinued  
We will assemble a cohort of clinical trials based on protocols approved by ethics committees from 2000 to 2003. We will determine the risk of discontinuation due to insufficient recruitment and compare them with trials that were completed and thus identify characteristics of study protocols associated with discontinuation due to poor recruitment. Finally, we will examine the publication history of trials that were discontinued, and assess to what extent lessons learned have been disseminated. We will extract relevant data from the files of collaborating ethics committees and from published trial reports, and through a survey of trialists. The study will be based on over 1000 protocols of clinical trials, and about 150 trials that were discontinued due to poor recruitment.  
Start of project: 01.02.2011 - End of project: 30.09.2014

Pre-specified subgroups in randomised trials DISCO 1 – subproject 5*  
The objective of this study is to investigate subgroup planning and reporting based on RCT protocols that were approved by six research ethics committees in three countries and the corresponding publications. Specifically, we will examine the agreement between statements about pre-specification in the publication and corresponding statements in the protocols.  
Start of project: 02.01.2012 - End of project: 30.04.2014

Research Projects in Surgery

The prognostic value of troponin T for long-term outcome after cardiac surgery:  
Following cardiac surgery, elevations in troponin I or troponin T, a marker of ischemic heat damage may be associated with increased short time risk (30 days) for a cardiac event, but data from long-term follow-up are missing. This study will provide information on the predictive value of troponin T levels after cardiac surgery for 30-day and one-year mortality. Data from a consecutive sample of patients who undergo cardiac bypass or valvular surgery at the University Hospital Basel from January 2007 to December 2010 will be analysed. Results from this study may improve perioperative risk assessment in cardiac surgery patients.  
Start of project: 01.01.2009 - End of project: 30.04.2014

Impact of examinees’ stereopsis and near visual acuity on laparoscopic virtual reality performance:  
Laparoscopic surgery represents specific challenges such as the reduction of a three-dimensional anatomic environment to two dimensions. We aimed at investigating the impact of the loss of the third dimension on laparoscopic virtual reality (VR) performance. We compared examinees with impaired to examinees with accurate stereopsis. The primary outcome was the difference between the mean total score of all tasks and the performance in a task testing eye-hand coordination, which was a priori considered to be the most dependent on intact stereopsis. We were unable to demonstrate an impact of impaired examinees’ stereopsis on laparoscopic VR performance. Individuals with accurate stereopsis seem to be able to compensate for the loss of the third dimension in laparoscopic VR simulations.  

Surgery for ischemic colitis: outcome and risk factors for in-hospital mortality:  
Surgery for ischemic colitis is associated with high perioperative morbidity and mortality, but the risk factors for mortality and surgical complications are unclear. In this retrospective single institution cohort study of all patients undergoing colorectal surgery for histologically proven
ischemic colitis between January 2004 and December 2010, we will evaluate surgical outcomes and pre-specified candidate risk factors for in-hospital mortality and major surgical complications. 

**Start of project: 05.05.2011 - End of project: 31.01.2014**

**Functional results after chest wall stabilization with a new screwless fixation device**

The aim of this study is to describe the experience in two surgical centres with a new screwless fixation device for the management of two types of rib fractures: flail chest and multiple dislocated rib fractures with significant chest wall deformity. 


**Designing questionnaires: healthcare survey to compare two different response scales**

A widely discussed design issue in patient satisfaction questionnaires is the optimal length and labelling of the answering scale. The aim of the present study was to compare intra-individually the answers to five general questions evaluating patients' perception of hospital care on an adjectival scale with three to four labelled categories to five redundant questions displayed on an 11-point end-anchored numeric scale. Since the longer scale did not substantially reduce the ceiling effect, the type of questions rather than the type of answering scale should be addressed with a focus on specific questions about concrete situations instead of general questions. Otherwise, further investigations are needed to find a more sensitive answering scale discriminating high-end ratings. 

**Start of project: 15.11.2011 - End of project: 31.07.2014**

**How to write a surgical clinical research protocol: literature review and practical guide**

Clinical research in studies involving surgical interventions presents some specific challenges. On the basis of a literature search of methodological literature and on some cardinal published surgical trials and observational studies, a 10-step guide for developing a surgical clinical study protocol was developed. The practical guide outlines key methodological issues important when planning an ethically and scientifically sound research project involving surgical interventions, with the ultimate goal of providing high-level evidence relevant for healthcare decision making in surgery. 

**Start of project: 05.07.2012 - End of project: 01.01.2014**

**Effect of different warm-up strategies on simulated laparoscopy performance: A randomised controlled trial**

The objective of this three-arm randomised controlled trial is to assess which type of warm-up has the highest effect on virtual reality laparoscopy performance. The following warm-up strategies are applied: a hands-on exercise (group 1), a cognitive exercise (group 2), and no warm-up (control, group 3). 

**Start of project: 26.07.2012 - End of project: 23.09.2014**

**Insurance Medicine**

**Disagreement in working assessment between disability claimants, treating physician and medical expert**

In this study we examine the level of (dis)agreement between treating physicians and an independent multidisciplinary team of physicians when assessing disability claimants' working ability. Treating physicians have a conflict of interest in assessing the working ability of their patients and may feel pressured to confirm their patients' own subjective working ability assessment in order not to harm their doctor patient relationship. We hypothesized that working ability assessment by treating physicians is similar to disability claimants' self-perception working ability and underestimates the working ability when compared to the assessment of an independent multidisciplinary team of physicians. 

**Start of project: 02.01.2012 - End of project: 28.02.2014**
HIV Infection, Swiss HIV Cohort Study and Multicohort Projects

Nonadherence as a predictor of mortality in HIV-infected individuals in the Swiss HIV Cohort Study (SHCS)*
Non-adherence to antiretroviral therapy (ART) is a predictor of virologic failure and development of drug resistance. The association between adherence and clinical outcomes such as progression to AIDS or death, however, is less well studied. This study will use novel techniques based on marginal structural models to estimate the causal effect of adherence to ART on all cause mortality. This method allows for better adjustment for time-dependent confounding by use of inverse probability weighting.
Start of project: 01.07.2009 - End of project: 31.03.2015

The CASCADE Study (Concerted Action on SeroConversion to AIDs or Death in Europe)±
CASCADE is a collaboration between investigators of European cohorts of HIV-infected patients with well-estimated dates of infection. Prof. Bucher serves as a member of the steering committee of CASADE and the institute is collaborating in various projects. For details see individual projects or www.CASCADE-Collaboration.org
Start of project: 01.01.2010 - End of project: 31.01.2016

Is an estimate from a multi-cohort collaboration necessarily better than an estimate from a single cohort study? Swiss HIV Cohort Study (SHCS)*
An estimate from an analysis by a multi-cohort collaboration may offer greater precision and less bias over an estimate from the analysis of data from a single cohort. However, these potential advantages will not necessarily be seen in practice. We will estimate the association between myocardial infarction and use of abacavir given the same SHCS data that a European multicohort collaboration included in its analysis of this association. We will also update our estimate using more recent versions of the SHCS database to compare gains in precision over time relative to those that can be achieved through cohort collaboration. We will consider whether such a collaboration was strictly necessary for an adequate estimate of this association.
Start of project: 01.01.2011 - End of project: 31.03.2015

Tenoforv in HIV-infected patients: A systematic review and meta-analysis of randomised controlled trials*
We assess in a systematic review and meta-analysis the benefit and side effects of tenoforv in HIV infected adults and children initiating antiretroviral therapy (ART).
Start of project: 01.01.2013 - End of project: 31.03.2015

Chronic hepatitis B and C co-infection and risk for the development of Non-Hodgkin lymphoma in HIV-infected patients: A multinational cohort study*
Despite the success of modern antiretroviral therapy Non-Hodgkin Lymphoma (NHL) continues to be an important cause of AIDS and AIDS related mortality in HIV-infected individuals. Hepatitis C (HCV) and Hepatitis B (HBV) co-infection is highly prevalent in HIV-infected individuals. We will investigate whether chronic HBV and HCV co-infection are associated with an increased risk of NHL and death, as there is growing evidence for such an association in HIV-negative population. This research question will be addressed using data from the Collaboration of Observational HIV Epidemiological Research in Europe study (COHERE in EUROCOORD).
Start of project: 01.06.2013 - End of project: 31.03.2015

Low level viremia under cART. The Swiss HIV Cohort Study (SHCS)*
For most patients with HIV, the amount of HIV in the blood declines rapidly with antiretroviral therapy and can no longer be detected. However for some patients, the virus either remains at a

*Project Leadership    ± Project Partner
low level or can occasionally be detected at a low level. We will investigate whether a persistent or repetitive low level of the virus is a precursor of the subsequent failure of therapy and the emergence of resistant mutations of the virus. Information from this project will enable clinicians to better judge the need for treatment change in patients with a low level of the virus. 
Start of project: 01.12.2013 - End of project: 31.03.2015

Optimizing HIV-RNA monitoring in naïve patients initiating ART. The Swiss HIV Cohort Study (SHCS)*
Guidelines recommend in patients receiving antiretroviral therapy (ART) routine life-long viral load (VL) monitoring every 3-6 months to timely detect virological failure, reduce the risk of resistant virus accumulation, enhance adherence and to assure patients. However, the optimal VL frequenting monitoring strategy is unknown which is of utmost relevance for resource-limited settings due to the high costs of VL monitoring. We aim to develop monitoring frequency optimization models from the Swiss HIV Cohort Study (SHCS) that will be relevant for resource limited settings to provide evidence-based guidance for optimal management and monitoring strategies of HIV-infected patients receiving ART.
Start of project: 01.03.2014 - End of project: 30.06.2015

Physical activity in patients with HIV over time. The Swiss HIV Cohort Study (SHCS)*
The prevalence of cardiovascular risk factors is high in patients infected with HIV. And while there is growing evidence that physical activity is safe and effective in improving cardiorespiratory fitness, metabolic profile and quality of life among patients with HIV, it is however not certain how physically active patients with HIV are. The aim of this study is to provide population-based estimates of the level of physical activity in patients with HIV and to show whether this level is changing over time. The average level of physical activity over time will be estimated for subgroups based on age, gender, stage of infection and CD4 cell count and will be explored with summary statistics and graphs.
Start of project: 01.09.2014 - End of project: 28.02.2015

HIV and non-HIV related morbidity and its associated resource use and costs in the Swiss HIV Cohort Study (SHCS): A data linkage pilot study*
There exists little data on costs and resource use for inpatient and ambulatory care and its main drivers in individuals with HIV infection in Switzerland. In this project of the Swiss HIV Cohort Study (SHCS) we will study the direct HIV and non-HIV related costs and resource use for inpatient and ambulatory care of HIV-infected individuals in Switzerland. We explore and assess factors such as late presentation, duration of HIV infection and others as predictors for high resource use and costs. This is a pilot and feasibility study where two completely anonymized data sets from the SHCS and claim data from Helsana will be matched with an encrypted method (Bloom filters) with birth dates, gender, and antiretroviral therapy being the matching variables.
Start of project: 01.10.2014 - End of project: 30.09.2015

Health Technology Assessment, Health Services Research and Ehealth
Evibox, a web-interface information system for mobile devices for search and implementation of evidence-based information for decision making at the bedside*
The aim of this project is to create a website that allows clinicians to access and create relevant risk calculator, scores and questionnaires through a modern and simple web-interface on mobile devices (i.e. iPhone, Android-Phones, iPad). The available tools shall be backed by clinical evidence where available. Further incorporation into clinical research and evaluation of its impact on clinical practice is planned. The website is currently redesigned and ported to the new angular JS framework for easier maintainability in the future.
Start of project: 01.11.2010 - End of project: 30.09.2015
EUnetHTA (European Network for Health Technology Assessment) Joint Action 2, Work package 7±

The EUnetHTA Collaboration aims to facilitate the efficient use of resources for Health Technology Assessment (HTA), to create a sustainable system for sharing HTA knowledge, and to promote good practice in HTA methods and processes in Europe. We participate in the EUnetHTA project WP-7 SG 3 and are involved in the development of a methodological guideline on the evaluation of non-randomised controlled trials' validity.

Start of project: 01.01.2013 - End of project: 31.12.2015

Methodological Research Projects

**Stopped trials early for benefit – trials published after a stopped trial – ethical? (STOP-IT 3)**

The study investigates how often randomised controlled trials (RCTs) are launched or completed after the publication of a trial stopped early for benefit addressing the same question. RCTs are stopped early for benefit because it is considered unethical to deprive patients in control groups from an intervention of obvious benefit. If new RCTs on the same research question are launched following the publication of trial stopped early for benefit the current practice in terms of stopping RCTs for apparent benefit might be considered as not sufficiently conservative. The project investigates the prevalence of this perception in the research community.

Start of project: 01.11.2009 - End of project: 30.06.2015

**Epidemiology and publication of discontinued randomised trials, DISCO 1**

- **Discontinued randomised trials in oncology, DISCO 1, subproject 2**
  The objective of this study is to investigate the use of validated quality of life instruments in randomised controlled trials (RCTs) in oncology. In addition, we will examine the epidemiology and publication history of RCTs in oncology based on a large sample of RCT protocols.

  Start of project: 25.11.2013 - End of project: 31.03.2015

- **Randomised versus non-randomised discontinued studies, DISCO 1, subproject 3**
  The objective of this study is to compare the prevalence and reasons for discontinuations between randomised controlled trials (RCTs) and non-randomised studies. We will do this based on a retrospective cohort of study protocols.

  Start of project: 05.08.2013 - End of project: 30.06.2015

- **Stopping rules in discontinued and completed trials, DISCO 1, subproject 4**
  Based on an international multicentre cohort of protocols from randomised controlled trials (RCTs) we aim to determine: (i) the prevalence of interim analyses, stopping rules and presence of a data safety monitoring board (DSMB) in completed and discontinued RCTs; (ii) trials characteristics associated with reporting of interim analyses, stopping rules and DSMBs; (iii) the proportion of discontinued trials with a matching stopping rule; (iv) discrepancies between planning and reporting of interim analysis, stopping rules and DSMBs.

  Start of project: 02.07.2012 - End of project: 28.02.2015

- **Intensive Care Trials, DISCO 1, subproject 6**
  The objective of this study is to determine the prevalence of, and reasons for, discontinuation of randomised controlled trials (RCTs) of critically ill patients. We will further explore the publication history of intensive care trials and the quality of reporting in peer-reviewed journals.

  Start of project: 05.05.2014 - End of project: 30.06.2015
**Discontinuation of randomised controlled trials in pediatrics, DISCO 1, subproject 7**
The objective of this study is to determine the prevalence of, and reasons for, discontinuation of randomised controlled trials (RCTs) in pediatrics. We will further explore the publication history of pediatric trials and the quality of reporting in peer-reviewed journals.
*Start of project: 03.03.2014 - End of project: 31.12.2015*

**Publication bias systematic reviews**
A series of systematic reviews (SRs) have the goal of elucidating the scope of non-publication and publication bias and are part of the OPEN Project (To Overcome failure to Publish nEGative fiNdings). In a first SR we seek to evaluate the extent of non-publication of research studies which were approved by ethics committees, registered in trial registries or presented as conference abstracts. A second SR aims to assess the impact of unpublished studies or those published in the grey literature on pooled effect estimates in meta-analyses. A third SR will summarise the epidemiology of SRs including in-vivo animal experiments and the frequency they consider and assess publication bias. And a fourth SR on methods to identify and handle publication bias.
*Start of project: 03.12.2012 - End of project: 28.02.2015*

**REporting of studies Conducted using Observational Routinely-collected Data (RECORD): A systematic review**
This project seeks to evaluate if the results of studies of routinely collected health data (e.g. from electronic health records, administrative claims, or patient registries) are adequately reported in scientific journals. This research provides an empirical foundation to inform the RECORD (REporting of studies Conducted using Observational Routinely-collected Data) initiative, which aims to develop a reporting guideline for studies using routinely collected data. Such reporting guidelines should reduce future incomplete or unusable reporting of biomedical research.
*Start of project: 01.01.2013 - End of project: 30.06.2015*

**Do routinely collected health data complement randomised evidence? A survey**
Observational studies using routinely collected (health) data (RCD-studies) are essential for comparative effectiveness research (CER) to close important gaps when information from randomised controlled trials (RCTs) is missing. Evidence from RCD-studies may be sooner available than from RCTs, based on larger sample sizes and allow for more indepth analysis of subgroup effects in patient populations frequently underrepresented in RCTs. Routinely collected data (RCD) are proposed to complement RCTs for comparative effectiveness research and to inform health care decisions when RCTs would be unfeasible. We conduct an empirical analysis of RCD-studies to assess how frequent they really address such gaps in evidence and provide answers on previously unanswered questions in health care.
*Start of project: 20.03.2013 - End of project: 28.02.2015*

**Concordance of treatment effects of ‘real world’ observational data using marginal structural models and randomised controlled trials: A meta-epidemiological study**
Marginal structural models (MSMs) are increasingly used to address confounding issues in biomedical research. This meta-epidemiological study seeks to explore whether modern MSM-based analyses of ‘real world’ observational data can be used to reliably guide health care decision making. We aim to identify potential factors or characteristics of ‘real world’ data sources, analytical approaches, or clinical topics which affect the reliability of observational data analyses. If possible, a list of criteria that affect the reliability of ‘real world’ observational data should be created that will inform future guideline development, health care decision making, and research.
*Start of project: 20.03.2013 - End of project: 31.12.2015*
Comparative treatment effects of on-label and off-label drug use: A meta-epidemiological study*
Off-label use of a drug refers to any application that is in deviation from the use approved by a drug licensing agency. Preferably off-label drug use should be considered when there is no alternative on-label treatment for a patient’s condition e.g. in case of serious conditions if approved drugs have failed. Off-label use is highly prevalent in medical practice but often not supported by good evidence. In this meta-epidemiological analysis the overall benefits and harms of off-label use is evaluated in comparison to licenced drugs used for the same indication.
Start of project: 10.12.2013 - End of project: 30.06.2015

Learning from failure - Understanding the mechanisms of trial discontinuation, DISCO 2, main project*
In a first project we will conduct semi-structured interviews with principal investigators of randomised controlled trials (RCTs) discontinued for insufficient recruitment and with key stakeholders of clinical research in Switzerland. A second project will examine health-care RCTs funded by the Swiss National Science Foundation to explore whether a rigorous selection of trials for funding and monitoring decreases the risk of trial discontinuation including potential effects of full versus partial funding. In a third project we will perform an analysis of recruitment patterns from about 500 completed and discontinued RCTs conducted in different countries and settings. It will explore whether insufficient recruitment can reliably be identified at an early stage and determine optimal time points and criteria for the assessment of recruitment progress in RCTs.
Start of project: 01.12.2013 - End of project: 30.11.2015

Reporting of discontinued trials DISCO 2, subproject 1*
The objectives of this empirical study are (i) to gather a comprehensive list of published root causes for randomised controlled trials (RCTs) discontinuation due to poor recruitment, (ii) to examine to what extent and how investigators of discontinued RCTs due to poor recruitment report results and lessons learned, and (iii) to investigate the proportion of actually recruited patients in relation to the target sample size in RCTs discontinued due to poor recruitment. We will use 3 different approaches in order to identify publications of RCTs discontinued due to poor recruitment: (1) subsample from the DISCO study; (2) search using the Medical Subject Heading (MeSH) term discontinued trial; and (3) a text word search.
Start of project: 07.01.2013 - End of project: 31.03.2015

Registered discontinued randomised controlled trials DISCO 2, subproject 2*
The objective of this project is to examine the comprehensiveness and reliability of the registry information on discontinued trials in order to assess its usefulness. In order to achieve this we will compare published reports from discontinued randomised controlled trials (RCTs) to information documented in trial registries.
Start of project: 15.01.2014 - End of project: 28.02.2015

Design features DISCO 2, subproject 3*
This study is a matched comparison between discontinued randomised controlled trials (RCTs) and completed RCTs. Based on key characteristics of the trials discontinued due to poor recruitment (i.e. patient population, intervention, comparator, and outcome) we will conduct systematic searches of electronic databases to identify similar RCTs that were completed as planned. We will then analyse the pairs of completed and discontinued RCTs for differences in design features, logistics, and trial conduct.
Start of project: 03.02.2014 - End of project: 30.09.2015
Longitudinal evaluation of the accuracy and completeness of clinical trial protocols - evidence for improvement*

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) were published in 2013 and the new Swiss Federal Law on Research in Humans (Humanforschungsgesetz, HFG) came into effect in January 2014. The present project aims to investigate the accuracy and completeness of clinical trial protocols approved by Research Ethics Committees before the introduction of SPIRIT and HFG and thereafter. In addition, we will evaluate the extent of appropriately registered protocols before the introduction of SPIRIT and HFG and thereafter (in national or international registries).

*Start of project: 07.11.2014 - End of project: 28.02.2017*

Infectious Diseases

Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV-infection*

We will update our Cochrane Review on adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV-infection.

*Start of project: 10.09.2010 - End of project: 31.03.2015*

Routine prescription feedback and peer comparison to lower antibiotic prescriptions in primary care - A pragmatic randomised controlled trial*

Excessive usage of antibiotics raise the emergence of resistant bacteria which poses an increasingly serious problem in Europe. The aim of this randomised controlled trial is to evaluate the effect of repeated postal/web-based feedbacks of individual antibiotic prescription rates on the prescription behaviour of primary care physicians in Switzerland with high prescription rates.

*Start of project: 01.01.2011 - End of project: 31.12.2015*

Efficacy and safety of low-dose corticosteroids in patients with community acquired pneumonia: Systematic review and individual patient-data meta-analysis of randomised trials±

We will undertake a systematic review and an individual patient-data (IPD) meta-analysis of all available randomised controlled trials (RCTs) to study the benefits and possible harms of using adjunctive low-dose corticosteroids in the treatment of patients with community acquired pneumonia (CAP). Specifically we will investigate whether treatment effects differ across pre-specified patient subgroups.

*Start of project: 06.02.2015 - End of project: 31.01.2016*

Intensive Care

Systematic review of studies comparing different vasopressor dosing strategies±

We systematically review studies in severe sepsis that specifically compare alternative strategies for the dosing of vasopressors. The main goal is to determine whether a more restrictive use of vasopressors improves clinical outcomes compared to liberal or standard use. We will include both clinical trials and controlled observational studies in humans. We will also include controlled animal experiments meeting minimal requirements of clinical relevance.

*Start of project: 01.01.2008 - End of project: 31.03.2015*

Investigation of continuous effect modifiers in a meta-analysis on higher versus lower positive end-expiratory pressure (PEEP) in ventilated patients with acute respiratory distress syndrome (ARDS)±

We will use the multivariable fractional polynomia interaction (MFPI) approach to investigate the interaction between continuous patient baseline characteristics (body mass index, Pa02/Fi02, respiratory compliance, and oxygenation index) and the allocated ventilation strategy (higher
versus lower PEEP). Outcomes of interest are in-hospital mortality (up to 60 days), time to death, time to unassisted breathing, and incidence of pneumothorax. Our intention-to-treat population consists of all patients randomly assigned to a higher or lower PEEP strategy upon initiation of the protocol. For each study MFPI provides a continuous treatment effect function. The function of each of the three studies will be averaged by a novel (new) meta-analysis approach.

**Start of project: 15.06.2010 - End of project: 30.06.2015**

### Anesthesiology

**Carbetocin trial**

Carbetocin is routinely given during caesarean section to improve uterine contraction with the aim of reducing blood loss. In this randomised, controlled double-blind non-inferiority trial we aim at comparing uterine tone and haemodynamic side effects of carbetocin when given as a slow bolus injection or as a short infusion. We assume that the effects on the uterus will not differ, but that especially cardiovascular side effects will be less pronounced after administration via short infusion.

**Start of project: 02.01.2012 - End of project: 31.12.2016**

**Effect of intraoperative infiltration with local anesthesia on the development of chronic pain after inguinal hernia repair: A randomised, triple-blinded, placebo-controlled trial**

Chronic pain is a common complication after inguinal hernia repair. The objective of this randomised, controlled, triple-blinded trial was to assess the effect of intraoperative infiltration with local anesthetic versus placebo on the development of chronic pain after repair of a single- or double-sided inguinal hernia. A logistic regression model using generalised estimating equations to adjust for clustering in bilateral hernias did not show any evidence that intraoperative infiltration of local anesthetic had an impact on the development of chronic postoperative pain.

**Start of project: 14.03.2012 - End of project: 05.01.2015**

### Metabolic Diseases and Nutrition

**Systematic reviews on lipid-modifying interventions**

We will conduct and update several systematic reviews and meta-analyses investigating the benefit and adverse events of fibrates, ezetimibe, and niacin in primary and secondary prevention of cardiovascular diseases.

**Start of project: 01.01.2009 - End of project: 31.12.2015**

**COCHRANE-Review: Early nutritional therapy for adult medical inpatients**

Although clinical nutrition is one of the most common interventions in medicine, there is no current standard algorithm for its use in acutely-ill medical inpatients at risk of malnutrition. The objective of the present project is to conduct a systematic review and meta-analysis of randomised controlled trials that evaluate the benefits and harms of early nutritional therapy for malnourished or nutritionally at-risk adult medical inpatients.

**Start of project: 01.05.2014 - End of project: 31.03.2015**

### Cardiovascular and Lung Diseases

**The Mannitol bronchial challenge test in the diagnosis of asthma**

The objective of this systematic review and meta-analysis will be to assess the diagnostic accuracy of the mannitol bronchial provocation test for the diagnosis of asthma in adults by pooling sensitivity, specificity, positive and negative predictive values, and likelihood ratios of diagnostic accuracy studies.

**Start of project: 06.08.2010 - End of project: 28.02.2015**
Colchicine for cardiovascular diseases (CVD): A systematic review and meta-analysis*

Recently published results from a randomised controlled trial indicate a potentially considerable benefit of low-dose colchicine treatment for secondary prevention of cardiovascular disease. In this project we systematically review and synthesize evidence on the effects of colchicine on cardiovascular outcomes.

Start of project: 23.04.2013 - End of project: 28.02.2015

Swiss Transplant Cohort Study

The Swiss Transplantation Cohort Study (STCS):±

The main objective of the STCS is to integrate and coordinate all information on transplant activities of solid and hematopoietic stem cell in Switzerland and to provide a base for observational and interventional high quality clinical research in transplantation medicine. The goal of this prospective cohort study is to improve patient management for organ transplantation in Switzerland. Our institute is responsible for the epidemiological support and central data management of this study.


A prospective evaluation of the infectious disease burden after solid organ transplantation in the Swiss Transplant Cohort Study (STCS):±

Infectious diseases (ID) complications are a main contributor to morbidity and mortality after solid organ transplantation. The true rates are often unknown, and if changes in rate and type are subtle, often go unnoticed. This study allows a concise assessment of the ID burden across all types of organ transplanted in Switzerland. Regular analysis will identify new trends, and serve as an invaluable quality control for each program.

Start of project: 08.11.2010 - End of project: 31.12.2015

Psychological profiles of living-donor compared to deceased-donor kidney allograft recipients. The Swiss Transplant Cohort Study (STCS):±

We suggest a primarily descriptive analysis of baseline psychosocial and demographic characteristics of living donor renal transplant recipients (LDRT) compared to deceased donor renal transplant recipients (DDRT) recipients enrolled in STCS. In a primarily descriptive analysis we will analyse psychosocial and demographic characteristics such as education, profession, working capacity, socio-economic status, quality of life (QoL) and depression of living donor renal transplant recipients (LDRT) compared to deceased donor renal transplant recipients (DDRT) enrolled in STCS. In a second step we will analyse the one-year post-transplant course of LDRT and DDRT recipients focusing on depression and QoL.

Start of project: 01.01.2012 - End of project: 31.12.2015

Impact of implantation of ventricular assist device (VAD) on the incidence of post-transplant infection in heart transplant recipients. The Swiss Transplant Cohort Study (STCS):±

Ventricular assist devices (VAD) are becoming a valuable therapeutical option for patients with heart failure refractory to medical therapy while awaiting heart transplantation. Patients on VAD have a increased chances of survival and quality of life than patients on medical therapy but are at high risk for infection after implantation of a VAD. We will assess the incidence, epidemiology and clinical characteristics of post transplant infections in heart transplant recipients with or without a VAD and investigate the correlation between VAD related infections and post-transplant outcome.

Start of project: 06.02.2012 - End of project: 31.12.2015
Epidemiology of fungal infection in the Swiss Transplant Cohort Study (STCS)

Invasive fungal infections (IFI) are a leading cause of morbidity and mortality in solid organ transplant (SOT) recipients. Epidemiology and risk factors of fungal infection and colonization differ between type of transplanted organ and pathogens. The primary aim of this study is to describe the epidemiology of infection and colonization with Apergillus spp., Candida spp., Pneumocystis jirovecii and rare fungi in SOT recipients of the STCS.

Start of project: 30.06.2012 - End of project: 30.06.2015

Oncology

[90Yttrium-DOTA]-TOC and [177Lutetium-DOTA]-TOC in metastasized neuroendocrine cancers: a cohort study

There is no standard treatment for highly-differentiated neuroendocrine cancers. In a single-center, open-label study, we will investigate in a large cohort of over 1500 patients with progressive metastasized neuroendocrine cancer the response, survival, and safety profile of [90Yttrium-DOTA]-TOC, [177Lutetium-DOTA]-TOC and the combined treatment of [90Yttrium-DOTA]-TOC plus [177 Lutetium-DOTA]-TOC. We will use Cox regression and competing risk regression models.

Start of project: 01.01.2010 - End of project: 30.06.2015

Systematic Review and individual patient data (IPD) meta-analysis of elderly primary central nervous system (CNS) lymphoma patients

This systematic review and individual patient data meta-analysis will investigate the effectiveness of first line treatments in primary CNS lymphoma patients aged 60 and over in relation to the applied chemotherapy applied tumor response, progression free and over all survival.

Start of project: 06.01.2011 - End of project: 09.02.2015

Use of heparin for cancer: individual patient data meta-analysis

Study level systematic reviews on this topic indicate a reduction in venous thromboembolism and provide moderate confidence that a small survival benefit exists. We will perform an individual patient data meta-analysis (IPDMA) to explore the magnitude of the suggested survival benefit and address whether or not specific subgroups and characteristics of cancer patients are more likely to benefit from parenteral anticoagulants.

Undergraduate
University of Basel

H. C. Bucher, M. Briel, M. T. Koller and A. J. Nordmann teach principles of evidence-based medicine, critical appraisal skills, basics in clinical epidemiology and clinical research methodology to medical students in the bachelor and masters program at the University of Basel. Total teaching obligations in 2014 were 130 hours.

Postgraduate
University of Basel

1. H. C. Bucher. Öffentliche Gesundheit: Screening, Institute of Nursing Science, University of Basel, 14.05.2014 (6 hours).
2. M. Briel. Systematische Reviews und Meta-Analysen, GCP Aufbaukurs Sponsor-Investigator 2014, Clinical Trial Unit, Departement Klinische Forschung, University Hospital Basel, 26.03.2014 and 10.09.2014 (1 hour each).
3. M. Briel, T. Fabbro, S. von Felten. Von der Forschungsfrage zur Studie, GCP Aufbaukurs Sponsor-Investigator 2014, Clinical Trial Unit, Departement Klinische Forschung, University Hospital Basel, 26.03.2014 (1 hour).

Other Academic Institutions

1. M. Briel. Systematic Review Methods, online course, McMaster University Hamilton, Ontario, Canada, 10.01 - 30.04. 2014 (100 hours).
2. M. Briel. Qualitätsbewertung klinischer Studien, presentation at the workshop „Systematische Übersichtsarbeiten“, German Cochrane Centre, Freiburg, Germany, 20.-22.03.2014 (1 hour).

PhD Students (Epidemiology)

1. M. Briel MD, Epidemiology and determinants of randomized controlled trials discontinued for insufficient recruitment of participants, 2013-2016.

Supervision of Masters Theses

1. R. Al Turkii. Faculty of Science, Epidemiology, University of Basel, supervised by M. Briel.
2. A. Amstutz. Faculty of Medicine, University of Basel, supervised by M. Briel.
3. A. Arpagaus. Faculty of Medicine, University of Basel, supervised by L. G. Hemkens.
4. J. E. Bühler. Faculty of Medicine, University of Basel, supervised by L. G. Hemkens.
5. R. Frei. Faculty of Medicine, University of Basel, supervised by M. Briel.
6. T. Jakob. Faculty of Medicine, University of Basel, supervised by A. J. Nordmann.
7. A. Rohner. Faculty of Medicine, University of Basel, supervised by A. J. Nordmann.
8. A. Ladanie. Faculty of Science, Epidemiology, supervised by H. C. Bucher and L. G. Hemkens.
9. J. Surina. Faculty of Science, University of Tübingen, Germany, supervised by M. Briel.
# Staff as of December 31, 2014

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<thead>
<tr>
<th>Name</th>
<th>Position</th>
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<tbody>
<tr>
<td>Prof. Heiner C. Bucher, MD, MPH</td>
<td>Head of Institute</td>
<td>100%</td>
</tr>
<tr>
<td>Sonja Achermann, Business Economist</td>
<td>Business Administrator</td>
<td>60%</td>
</tr>
<tr>
<td>Assistant Prof. Matthias Briel, MD MSc</td>
<td>Senior Scientist</td>
<td>Associated collaborator</td>
</tr>
<tr>
<td>Dr. Salome Dell-Kuster, MD, MSc</td>
<td>Biostatistician</td>
<td>40%</td>
</tr>
<tr>
<td>Hannah Ewald, MPH</td>
<td>Research Associate</td>
<td>100%</td>
</tr>
<tr>
<td>Dominik Glinz, PhD</td>
<td>Research Associate</td>
<td>100%</td>
</tr>
<tr>
<td>Viktoria Gloy, PhD</td>
<td>Research Associate</td>
<td>60%</td>
</tr>
<tr>
<td>Daniel Good, BSc (FH)</td>
<td>Assistant Data Manager</td>
<td>Associated collaborator</td>
</tr>
<tr>
<td>Lars Hemkens, MD, MPH</td>
<td>Senior Scientist</td>
<td>100%</td>
</tr>
<tr>
<td>Assistant Prof. Michael Koller, MSc</td>
<td>Senior Scientist</td>
<td>Associated collaborator</td>
</tr>
<tr>
<td>Aviv Ladanie, BSc</td>
<td>Master Student in Epidemiology</td>
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<tr>
<td>Sandra Manz, BA</td>
<td>Administrative Assistant</td>
<td>40%</td>
</tr>
<tr>
<td>Prof. Alain Nordmann, MD, MSc</td>
<td>Senior Scientist</td>
<td>10%</td>
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<tr>
<td>Kübra Oezoglu, BSc</td>
<td>Student Aid</td>
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<tr>
<td>Heike Raatz, MD, MSc</td>
<td>Senior Scientist</td>
<td>80%</td>
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<tr>
<td>Juliane Rick, Qualified Biomathematician (FH)</td>
<td>Data Manager</td>
<td>Associated collaborator</td>
</tr>
<tr>
<td>Ramon Saccilotto, MD, MAS</td>
<td>Research Associate</td>
<td>Associated collaborator</td>
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<tr>
<td>Juliane Schäfer, PhD</td>
<td>Biostatistician</td>
<td>60%</td>
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<tr>
<td>Stefan Schandlmaier, MD</td>
<td>Research Associate</td>
<td>80%</td>
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<tr>
<td>Prof. Pedram Sendi, MD, DMD</td>
<td>Senior Scientist</td>
<td>Associated collaborator</td>
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<tr>
<td>Susanne Stampf, PhD</td>
<td>Biostatistician</td>
<td>Associated collaborator</td>
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<tr>
<td>Sarah Thommen, MSc</td>
<td>Junior Biostatistician</td>
<td>80%</td>
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<tr>
<td>Madeleine Wick, MS Pharm, MPH</td>
<td>Study Coordinator</td>
<td>Associated collaborator</td>
</tr>
<tr>
<td>Jim Young, PhD</td>
<td>Senior Biostatistician</td>
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<td>Description</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>37</td>
<td>Report of the Statutory Auditor 2014</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>Balance Sheet as of December 31, 2014</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>Profit and Loss Account for the Fiscal Year from January 1, 2014 to December 31, 2014</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Notes to the Annual Financial Statements</td>
<td></td>
</tr>
</tbody>
</table>
REPORT OF THE STATUTORY AUDITOR 2014

Report of the statutory auditors
on the limited statutory examination
to the Board of
Stiftung Institut für klinische Epidemiologie
Basel

As statutory auditors, we have examined the financial statements of Stiftung Institut für klinische Epidemiologie, which comprise the balance sheet, income statement and notes, for the year ended 31 December 2014.

These financial statements are the responsibility of the Board. Our responsibility is to perform a limited statutory examination on these financial statements. We confirm that we meet the licensing and independence requirements as stipulated by Swiss law.

We conducted our examination in accordance with the Swiss Standard on Limited Statutory Examination. This standard requires that we plan and perform a limited statutory examination to identify material misstatements in the financial statements. A limited statutory examination consists primarily of inquiries of foundation personnel and analytical procedures as well as detailed tests of foundation documents as considered appropriate in the circumstances. However, the testing of the operational processes and the internal control system, as well as inquiries and further testing procedures to detect fraud or other legal violations, are not within the scope of this examination.

Based on our limited statutory examination, nothing has come to our attention that causes us to believe that the financial statements do not comply with Swiss law and the foundation’s deed.

PricewaterhouseCoopers AG

Afons Furrer
Audit expert
Auditor in charge

Heribert Riesterer
Audit expert

Basel, 21 May 2015
<table>
<thead>
<tr>
<th></th>
<th>December 31, 2014</th>
<th>December 31, 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assets</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Current Assets</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cash and investments</td>
<td>1’220’000.00</td>
<td>1’557’789.83</td>
</tr>
<tr>
<td>Debtors</td>
<td>0.00</td>
<td>4’488.80</td>
</tr>
<tr>
<td>Work in process</td>
<td>0.00</td>
<td>56’986.80</td>
</tr>
<tr>
<td>Prepaid expenses and deferred</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>charges</td>
<td></td>
<td></td>
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<tr>
<td><strong>Total Current Assets</strong></td>
<td>1’220’000.00</td>
<td>1’619’265.43</td>
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<tr>
<td><strong>Fixed Assets</strong></td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Hardware</td>
<td>0.00</td>
<td>p.m.</td>
</tr>
<tr>
<td>Furniture and office equipment</td>
<td>0.00</td>
<td>p.m.</td>
</tr>
<tr>
<td><strong>Total Fixed Assets</strong></td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>TOTAL ASSETS</strong></td>
<td>1’220’000.00</td>
<td>1’619’265.43</td>
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<tr>
<td><strong>LIABILITIES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Liabilities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accounts payable</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
<td>Deferred income</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
<td>Accrued liabilities</td>
<td>30’000.00</td>
<td>30’000.00</td>
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<tr>
<td><strong>Total Liabilities</strong></td>
<td>30’000.00</td>
<td>30’000.00</td>
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<tr>
<td><strong>Endowment Fund</strong></td>
<td></td>
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<tr>
<td>Endowment capital</td>
<td>150’000.00</td>
<td>150’000.00</td>
</tr>
<tr>
<td>Contributions from Bangerter-Stiftung</td>
<td>1’020’000.00</td>
<td>1’020’000.00</td>
</tr>
<tr>
<td>Net Income 2014/Profit carried forward</td>
<td>20’000.00</td>
<td>419’265.43</td>
</tr>
<tr>
<td><strong>Total Endowment Fund of the Foundation</strong></td>
<td>1’190’000.00</td>
<td>1’589’265.43</td>
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<tr>
<td><strong>TOTAL LIABILITIES</strong></td>
<td>1’220’000.00</td>
<td>1’619’265.43</td>
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</tbody>
</table>
## PROFIT AND LOSS ACCOUNT FOR THE FISCAL YEAR FROM JANUARY 1, 2014 TO DECEMBER 31, 2014

### INCOME

<table>
<thead>
<tr>
<th>Description</th>
<th>2014</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Income from research projects</td>
<td>0.00</td>
<td>916,319.04</td>
</tr>
<tr>
<td>Contributions from Santésuisse</td>
<td>0.00</td>
<td>200,000.00</td>
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<tr>
<td>Contributions from Bangerter-Stiftung</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Funding by the University of Basel and donations</td>
<td>20,000.00</td>
<td>173,977.30</td>
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<tr>
<td>Other income</td>
<td>6,350.00</td>
<td>2,034.62</td>
</tr>
<tr>
<td>Extraordinary income</td>
<td>0.00</td>
<td>120,000.00</td>
</tr>
<tr>
<td><strong>TOTAL INCOME</strong></td>
<td><strong>26,350.00</strong></td>
<td><strong>1,412,330.96</strong></td>
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</tbody>
</table>

### CHARGES

<table>
<thead>
<tr>
<th>Description</th>
<th>2014</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wages and salaries</td>
<td>0.00</td>
<td>1,388,843.49</td>
</tr>
<tr>
<td>Information technology</td>
<td>0.00</td>
<td>5,082.25</td>
</tr>
<tr>
<td>Depreciation</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Expenses for administration and third party counselling</td>
<td>6,350.00</td>
<td>48,980.28</td>
</tr>
<tr>
<td>Travelling and congress attendances</td>
<td>0.00</td>
<td>6,980.05</td>
</tr>
<tr>
<td>Advertising and public relations</td>
<td>0.00</td>
<td>16,408.09</td>
</tr>
<tr>
<td>Other operating charges</td>
<td>0.00</td>
<td>15,647.58</td>
</tr>
<tr>
<td><strong>TOTAL CHARGES</strong></td>
<td><strong>6,350.00</strong></td>
<td><strong>1,481,059.74</strong></td>
</tr>
</tbody>
</table>

### NET INCOME (NET LOSS) FOR THE YEAR

<table>
<thead>
<tr>
<th>Description</th>
<th>2014</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net income (Net loss)</td>
<td>20,000.00</td>
<td>-68,728.78</td>
</tr>
</tbody>
</table>

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39
1. Establishment and Organisation of the Foundation

1.1 Name
The Foundation Institute for Clinical Epidemiology (“Stiftung Institut für klinische Epidemiologie” is established as a non-profit foundation in accordance with Article 80 et seq. of the Swiss Civil Code. The Foundation has its legal seat in Basel. The foundation charter is dated May, 29th, 2001. The foundation is tax-exempted.

1.2 Purpose
Purpose of the Foundation is to improve research in the field of clinical epidemiology and biostatistics. In particular, this aim shall be reached by establishing and operating the Basel Institute for Clinical Epidemiology and Biostatistics. The Basel Institute for Clinical Epidemiology and Biostatistics conducts and improves clinical research dealing with questions that are of practical relevance for frequent diseases and health problems. The Institute makes public practical knowledge of clinical research and public health, evaluates research methods and conducts clinical trials on issues of health economics. The Institute is involved in teaching clinical epidemiology and in the knowledge transfer of evidence based medicine in education and in the training, in particular, of medical doctors.

1.3 Governing Bodies
The Foundation’s governing bodies are the Board of Trustees, the Scientific Advisory Board and the external auditors. Each board, the Board of Trustees and the Scientific Advisory Board consists of a minimum of three members.

Board of Trustees December 31, 2014
Reto Guetg, MD, President
Prof. Joerg D. Leuppi, MD, Member
lic.rer.pol. Stefan Kaufmann, Member
Resignation as per December 31, 2014: lic.jur. Thomas Plattner

Two Board Members are authorised to sign collectively on behalf of the Foundation. The members of the Board of Trustees are voluntarily active. No fees are granted to members of the Board of Trustees.

Scientific Advisory Board
Prof. M. Tanner PhD, Swiss Tropical and Public Health Institute, Basel
Prof. A. Knottnerus, MD, University of Maastricht, The Netherlands
Prof. A. Detsky, MD, University of Toronto, Canada

Head of Institute
Prof. Heiner C. Bucher, MD, MPH

External Auditors
PricewaterhouseCoopers AG, Basel

Personnel
The Foundation does not employ any personnel.
1.4 Basel Supervisory Authority (BVG- und Stiftungsaufsicht beider Basel, BSABB)

The Foundation is supervised by the “BVG- und Stiftungsaufsicht beider Basel” (BSABB), Basel (the “Basel Supervisory Authority”). The Financial Statements 2012 and the Annual Report 2012 have been accepted by way of a disposition dd. May 16th, 2014. The disposition contained a remark with regard to the fact whether or not fees are granted to the Board of Trustees. The Financial Statements 2013 and the Annual Report 2013 have been filed with the Basel Supervisory Authority in good time. At the time of printing the Foundation was not in the possession of the corresponding disposition.

2. Notes to the Balance Sheet and to the Profit and Loss Account

2.1 General

In connection with the legal independence of the University Hospital of Basel, the Board of Trustees decided to outsource activities and that as from January 1st, 2014 third party funds acquired by the Institute’s head and collaborators shall be shown in the financial statements of the University Hospital of Basel. Therefore, the positions as presented in the following table of the Foundation's Financial Statements as of December 31, 2013 have been transferred to the University Hospital of Basel (as per January 1, 2014):

<table>
<thead>
<tr>
<th>Assets</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cash and investments</td>
<td>357'789.83</td>
</tr>
<tr>
<td>Debtors</td>
<td>4'488.80</td>
</tr>
<tr>
<td>Work in process</td>
<td>56'986.80</td>
</tr>
<tr>
<td></td>
<td><strong>419'265.43</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liabilities</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profit carried forward</td>
<td><strong>419'265.43</strong></td>
</tr>
</tbody>
</table>

Donations, legacies and other contributions in favour of the Foundation will be shown in the Foundation's annual accounts.

Starting with the financial year 2014, only the endowment fund, its investment, accrued liabilities and liabilities, if any, will be shown in the Foundation’s financial statements. Further, only such items of revenue and costs, respectively, arising from the Foundation’s remaining operating activities will be stated in its profit and loss account.

As of December 31, 2014 cash and investments (CHF 1’220’000.00) of the Foundation were deposited in the general Third Party's Fund of the University Hospital of Basel (“Drittmittelfonds des Universitätsspital Basel”). Direct investment in the Foundation’s name will take place within 2015. Further, in 2015 the Fluctuation Reserve (“Schwankungsreserve”) of said Third Party's Fund that is attributable to the Foundation’s Endowment Fund will flow to the Foundation.

2.2 Notes to the Investment of Assets (until December 31, 2014)

Until December 31, 2014, investments of assets have been handled on a fiduciary basis centrally by the Third Party's Fund of the University Hospital of Basel. The objective of the collective investment of funds is to optimise earnings without any loss of net asset value and to minimise costs.
As a rule, investments will be made in securities issued by first rate companies and first rate debtors or approved investment funds only. In terms of a balanced risk diversification investments may be restricted (debt securities – unlimited; shares – 20% of the total assets of the Third Party’s Fund; shares of real estate funds – 5%; and since 2012, precious metals – 3%).

Investments are valued at the market value at maximum on the balance sheet date.

Provisions have been accrued for any potential loss contingencies in the Third Party’s Fund (for investments in foreign currency up to 20%; for investments in shares and shares of investment funds up to 25%).

Annually the administration of the Third Party’s Fund (“Steuerungsausschuss Fonds”) decides on the appropriation of the balance sheet profit resulting from the collective investments. The average yield in 2013 was minus 1.83 % (in 2012: plus 3.07%). Losses will be covered by the Fluctuation Reserve (comprising the provisions, profit/loss carried forward and hidden reserves, if any).

3. Risk Evaluation

The Board of Trustees examens on a regular bases together with the head of the Institute the operative and strategic risks associated with the business activities. Appropriate measures are discussed.