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Dear reader

Since 15 years the Basel Institute for Clinical Epidemiology and Biostatistics (CEB) is providing excellent research with an outstanding team of very dedicated scientists. The scientific output over all this time and also in 2015 has been excellent. CEB is an interdisciplinary team and is living the spirit of collaboration with partners at the local, national and international level. This is particularly reflected in this years’ list of publication including research findings from such collaborations being published in the most prominent journals like the New England Journal of Medicine or the Lancet.

CEB is an associated institute of the University of Basel and was founded in 2001 together with the foundation ‘Stiftung Institut für Klinische Epidemiologie’. Thus, the University of Basel established the chair of clinical epidemiology and the foundation provided the core funding and funding for the infrastructure. This set-up made a start-up like organisation of the institute necessary with a very professional financial and project management. The institute achieves close to 90% of funding but more financial support is needed to increase the core funding and to guarantee the further success of CEB. The Board of Trustees of the Foundation is therefore actively looking for donors to support the institute.

My thanks go to the entire team of CEB for its outstanding performance in research, Health Technology Assessment (HTA) and teaching of the principles of evidence-based medicine. I also would like to thank Professor Bucher for his continuous enthusiasm and leadership.

Reto Guetg MD
President of the Board of Trustees
Foundation Institute for Clinical Epidemiology
The Board of Trustees
Prof. Jörg D. Leuppi MD PhD, Stefan Kaufmann, Dr. Reto Guetg MD
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 and added value for the health care system.
- We generate and appraise evidence of medical interventions by conducting own research for prevalent and important conditions and by synthesing evidence.
- We examine the effectiveness of new technologies in the real world setting by use of large cohort studies and registry data.
- We develop and teach the methods of evidence-based medicine to improve the quality of clinical research.

Our goal is 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.

Improve patient outcomes by evidence-based decision making and implementation of efficacious interventions into clinical care.

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.

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. We combine academic rigor, clinical knowledge and business acumen, allowing us to understand the specific needs for decision making at all health care levels. We provide high quality evidence for decision makers in health care, 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.
Effect of cumulating exposure to abacavir on the risk of cardiovascular disease events in patients from the Swiss HIV Cohort Study.


Background: Patients with HIV exposed to the antiretroviral drug abacavir may have an increased risk of cardiovascular disease (CVD) but it is not clear how that risk changes as exposure cumulates.

Methods and results: We assessed the effect of exposure to abacavir on the risk of CVD events in the Swiss HIV Cohort Study. We used a new marginal structural Cox model to estimate the effect of abacavir as a flexible function of past exposures while accounting for risk factors that potentially lie on a causal pathway between exposure to abacavir and CVD. A total of 11'856 patients were followed for a median of 6.6 years; 365 patients had a CVD event (4.6 events per 1'000 patient-years). In a conventional Cox model, recent - but not cumulative - exposure to abacavir increased the risk of a CVD event. In the new marginal structural Cox model, continued exposure to abacavir during the past 4 years increased the risk of a CVD event (hazard ratio = 2.06; 95% confidence interval: 1.43 to 2.98). The estimated function for the effect of past exposures suggests that exposure during the past 6–36 months caused the greatest increase in risk.

Conclusions and relevance: Abacavir increases the risk of a CVD event: the effect of exposure is not immediate, rather the risk increases as exposure cumulates over the past few years. This gradual increase in risk is not consistent with a rapidly acting mechanism, such as acute inflammation.

An analysis of protocols and publications suggested that most discontinuations of clinical trials were not based on preplanned interim analyses or stopping rules.


Background: We investigated the frequency of interim analyses, stopping rules, and data safety and monitoring boards (DSMBs) in protocols of randomised controlled trials (RCTs) and explored discrepancies in reporting between protocols and publications.

Methods and results: We used data from RCT protocols approved between 2000 and 2003 by six research ethics committees in Switzerland, Germany, and Canada. Of 894 RCT protocols, 289 prespecified interim analyses (32.3%), 153 stopping rules (17.1%), and 257 DSMBs (28.7%). Overall, 249 of 894 RCTs (27.9%) were prematurely discontinued; mostly due to poor recruitment, administrative reasons, or unexpected harm. 46 of 249 RCTs (18.4%) were discontinued due to early benefit or futility; of those, 37 (80.4%) were stopped outside a formal interim analysis or stopping rule.

Conclusions and relevance: Two-thirds of RCT protocols did not consider interim analyses, stopping rules, or DSMBs. Most RCTs discontinued for early benefit or futility and were stopped without a prespecified mechanism.

Definition and Classification of Intraoperative Complications (CLASSIC): Delphi Study and Pilot Evaluation.


Background: Standardized reporting of intraoperative adverse events is important to enhance transparency and to improve reporting of surgical outcome. There is no validated definition and classification of intraoperative complications.

Methods and results: We conducted a Delphi study to develop a definition and classification of intraoperative complications. 40 of 52 experts (77 % return rate) from 14 countries participated in this Delphi study which resulted in a comprehensive definition of intraoperative complications. The classification foresees four grades depending on the need for treatment (no need, grade I; need for treatment, grade II) and the severity of the complication (life-threatening/permanent disability, grade III; death, grade IV). The pilot study showed good practicability and a high agreement (intraclass correlation coefficient of 0.83 (95 % CI 0.73-0.90)).

Conclusions and relevance: In a Delphi process we develop definitions and classification of intraoperative complications by severity and will validate this tool in a next study with the ultimate goal to contribute to standardized reporting in surgical practice and research.
IMPACT OF RESEARCH FROM CEB

The h-Index
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

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<th>Senior Researcher</th>
<th>h-Index</th>
<th>Standard value</th>
<th>Mean citation frequencies per publication</th>
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<td>PD Dr. M. Briel</td>
<td>32</td>
<td>2.9</td>
<td>35.9</td>
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<tr>
<td>Prof. H.C. Bucher</td>
<td>50</td>
<td>2.5</td>
<td>37.8</td>
</tr>
<tr>
<td>PD Dr. M.T. Koller</td>
<td>19</td>
<td>1.6</td>
<td>21.9</td>
</tr>
<tr>
<td>Prof. A. Nordmann</td>
<td>20</td>
<td>1.6</td>
<td>28.2</td>
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1 The h-index starting from an author's first publication allows to evaluate the performance of a single researcher and summarizes the publication and citation frequency in one figure. For example a 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. A 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.

Citation frequency
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.

Figure 1. Citation frequency and number of indexed publications of senior researchers of CEB from 2001 to 2015 (Thompson Science Citation Index)
CEB RESEARCH

CEB has published in 2015 46 publications in peer reviewed journals some of them in high ranked journals like New England Journal of Medicine, Clinical Infectious Disease, 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 on methodological issues dealt with missing participant data in trials of meta-analysis (publication 1), limitations in meta-analyses to report absolut effect sizes (2), and the development of a classification system for intraoperative complications (30). We have continued our methodological research addressing the reasons for the premature discontinuation of clinical trials and the consistency of reporting reasons of discontinuation in trial protocols and publications (34, 35, 40).

Our expertise in systematic reviews is well reflected in a large number of publications. We investigated the comparative effectiveness of the antiretroviral drug tenofovir in treatment naïve HIV-infected patients (18). We contributed to a meta-analysis on nutrition support in malnourished hospitalised patients (4), a systematic review on target blood pressure for vasopressor therapy (9), and a meta-analysis on the association of air pollution and diabetes (13). We have also updated our systematic review in the Cochrane Library on the benefits of corticosteroids for the treatment of Pneumocystis jiroveci pneumonia in HIV infection (12).

We contributed to an individual patient data meta-analysis (IPD) investigating different ventilation techniques in intubated intensive care patients to reduce the risk of adult respiratory distress syndrome (3) and conducted another IPD on first-line treatment and outcome of elderly patients with primary central nervous system lymphoma (19). We collaborated in a meta-analysis (39) and a large clinical trial showing the benefit of adjunctive corticosteroids in patients under antibiotic treatment for pneumonia (5).

We collaborated in two studies investigating radiotherapeutics, yttrium-90-DOTATOC and lutetium-177-DOTATOC in progressive meningioma, and the somatostatin based radiopeptide therapy with (90) Y-DOTATOC versus (90) Y-DOTATOC plus (177) Lu-DOTATOC in metastasized gastrinoma (24, 11).

Our results from an observational data analyses in HIV show that non-adherence to antiretroviral therapy is associated with an increased risk of AIDS or death when investigated with a causal model (15). We further showed that transient low level viremia (viral blips) in antiretroviral treated patients may be associated with virological failure, a very important finding for longterm care in HIV (46). We also identified an increased risk of cardiovascular events with the cumulative exposure of the antiretroviral drug abacavir when using novel flexible marginal structural models, a finding which has not been shown by other investigators (43). An important study from our international collaboration investigated the immune status at time of linkage to care in Rwanda (28).

1 Number refers to the list of publication (see section “Publications of CEB in 2015”).
Team of Biostatisticians
Dr. Juliane Schäfer, Dr. Salome Dell-Kuster, Sarah Thommen
(Dr. James Young, absent,
Dr. Selene Leon Reyes, absent)

Clinical Epidemiology & Methodology Team
Dr. Benjamin Speich, Dimitry Gryaznow
Dr. Dominik Glinz, Kimberly McCord, Hannah Ewald,
Katherine Winkel, Kübra Oezoglu
Aviv Ladanie, Dr. Lars G. Hemkens
Prof. Heiner C. Bucher, PD Dr. Matthias Briel
(Prof. Alain Nordmann, absent,
Dr. Stefan Schandelmaier, absent)
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 master program at the University of Basel. Total undergraduate teaching obligations in 2015 were 126 hours. Collaborators of the institute participate in post-graduate clinical investigator courses.

CEB has contributed to five book chapters of the Users’ Guides to the Medical Literature. This manual for evidence-based clinical practice is among others edited by Gordon Guyatt the founder of evidence-based medicine, and Drummond Rennie, the former editor of JAMA.

CEB CONSULTING

Health Technology Assessment (HTA)

CEB is leading a consortium commissioned by the Swiss Medical Board for conducting HTA reports in Switzerland that involves academic partners from the University of Basel (European Center for Pharmaceutical Medicine) and other Swiss universities (Epidemiology, Biostatistics and Prevention Institute, University of Zurich, and the Institute Ethic Histoire Humanité, University of Geneva). We have finished the first report on operative versus conservative treatment of the acute and subacute lumboradicular syndrome due to herniated lumbar disc. CEB has consultancy mandates from the Swiss Federal Office of Public Health that are 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). CEB has initiated 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.
Clinical Methodological Research Consultancy Services
CEB is providing 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 5 publications (21, 30-32, 41) in 2015, 3 of them are methodological projects. For example, we have developed a classification system for intraoperative complications which will be validated in a future project (30).

Swiss Transplant Cohort Study
CEB was instrumental when the data centre of the Swiss Transplant Cohort Study (STCS) was founded in 2007. The staff of the data centre is associated with CEB. This large multicentre cohort study is collecting data on all solid organ transplantation in Switzerland and is funded by the Swiss National Science Foundation and the Swiss Federal Office of Public Health. By the end of 2015 the study has included 3’548 solid organ transplanted patients. There are more than 80 ongoing research projects and 20 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.
I would like to thank my entire team for the enthusiasm to advance our projects and for generating new research grants. CEB is extremely productive and is supported by an excellent team of secretaries and an administrator. To lead and work with such a team is a continuous source of inspiration, joy and a privilege.

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 documenting 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.

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. In a pilot project of the Swiss HIV Cohort Study we will address important questions on resource use. We conduct large scale pragmatic trials in primary care in Switzerland by use of claim data and address important questions such as optimizing the use of antibiotics in primary care.

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 some senior scientist holding clinical appointments - are the strengths of our consulting activities making us an attractive partner.
Original Publications in Peer Reviewed Journals


Research Letters, Letters and Non-Peer Reviewed Publications


Invited Editorials


(6) Suter K., Briel M., Günther J. Number needed to treat (NNT) and number needed to harm (NNH) - weitere Abkömmlinge der 4-Feldertafel. Med Monatsschr Pharm 2015; 38(3): 103-6.


Reports


(2) EunetHTA: European Network for Health Technology Assessment. Guideline: Internal validity of non-randomised studies (NRS) on interventions. Cologne, Germany: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) with assistance from Norwegian Knowledge Centre for the Health Services (NOKC), Norway and Swiss Network for Health Technology Assessment (SNHTA), Switzerland (including Raatz H.); July, 2015.

Book Chapters


Presentations

(1) Bucher H. C. Comparative Effectiveness Research: Potential für eine evidenz-basierte Patien-

tenversorgung. Universität Basel, Advanced Studies: "Spitalpharmazie und Klinische 


(2) Bucher H. C., Kanters S., O’Regan C. Maximazing value: realizing the potential of routinely 

collected data. ISPOR 18th Annual European Congress Milan, Italy: November 11, 2015.

(3) Bucher H. C. Principles of Evidence-Based Medicine (II). Heidelberg Health Economics 


(4) Bucher H. C., Briel M. Wie können Studienergebnisse von indirekten Vergleichen und Netz-

werk-Meta-Analysen besser in die klinische Entscheidungsfindung Eingang finden: Anleitung 

und Leitfaden für Kliniker und Patienten. 16. Jahrestagung des Deutschen Netzwerks für 


L. G. Colchicine for prevention of cardiovascular events: a systematic review and meta-analysis. 

day of Clinical Research, University Hospital Basel Basel, Switzerland: January 22, 2015.

(6) Hoffmann H., Delko T., Nebiker C., Kraljevic M., Schäfer J., Kettelhack C. Intestinal microper-

fusion patterns during colorectal resection: Preliminary results of 34 patients. 102. Jahrestagung 

der Schweizerischen Gesellschaft für Chirurgie Bern, Switzerland: May 20, 2015.

(7) Hoffmann H., Delko T., Nebiker Ch., Kraljevic M., Schäfer J., Kettelhack C. Intestinale Mikro-

perfusion während kolorektaler Resektionen. Erste Resultate von 34 Patienten. 9. Herbsttagung 

der Deutschen Gesellschaft für Allgemein-und Viszeralchirurgie gemeinsam mit der DGAV / 70. Jahrestag der Deutschen Gesellschaft für Gastroenterologie, Verdauungs-

und Stoffwechselkrankheiten mit Sektion Endoskopie Leipzig, Germany: September 16, 

2015.


Intraoperative microperfusion patterns during colorectal resection: Preliminary results of 22 

patients. 132. Kongress der Deutschen Gesellschaft für Chirurgie Munich, Germany: April 

28, 2015.

(9) Kasenda B., von Elm E., Young J., Blümle A., Tomonaga Y., Saccilotto R., Amstutz A., 

Bengough T., Meerpohl J. J., Stegert M., Tikkinen K. A. O., Neumann I., Carrasco-Labra A., 

Faulhaber M., Mulla S. M., Mertz D., Akl E. A., Bassler D., Busse J. W., Ferreira-Gonzales I., 

Lamontagne F., Nordmann A. J., Gloy V. L., Raatz H., Moja L., Rosenthal R., Ebrahim S., 

Schandelmaier S., Xin S., Vandvik P. O., Johnston B. C., Walter M. A., Burnand B., Schwenk-

glenks M., Hemkens L. G., Bucher H. C., Guyatt G. H., Briel M. Agreements on publication 

rights – An investigation of protocols and publications of randomized clinical trials. 23rd 

Cochrane Colloquium Vienna, Austria: October 5, 2015.

(10) Schandelmaier S., Conen K., von Elm E., Stegert M., Olu K. K., Gloy V. L., Raatz H., Schwenk-

glenks M., Hemkens L. G., Saccilotto R., Bucher H. C., Briel M., Kasenda B. Planning and 

reporting of quality of life outcomes in cancer trials. 23rd Cochrane Colloquium Vienna, 

Austria: October 5, 2015.


Posters and Abstracts


(3) Hemkens L. G., Contopoulos-Ioannidis D. G., Ioannidis J. P. Are routinely collected data studies reliable surrogates when there are no randomized trials? A meta-epidemiological study. 23rd Cochrane Colloquium Vienna, Austria: October 5, 2015.


HIV Infection, Swiss HIV Cohort Study and Multicohort Projects

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 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: 30.09.2015

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: 30.06.2015

Nonadherence as a predictor of mortality in HIV-infected individuals in the Swiss HIV Cohort Study (SHCS)*
Nonadherence 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: 30.09.2015

Methodological Research Projects

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

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: 31.05.2015

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

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. Further, a fourth SR on methods to identify and handle publication bias will be conducted.

Start of project: 03.12.2012 - End of project: 31.07.2015

HTA Reports

EUnetHTA (European Network for Health Technology Assessment) Joint Action 2, Workpackage 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

Leitlinie Endometriumkarzinom (Guideline on endometrial cancer)*

We prepare a systematic review on screening with transvaginal ultrasound for endometrial cancer for the S3 guideline on endometrial cancer on behalf of the group led by Prof. G. Emons, Leitlinienkoordination deutsche S3 Leitlinie Georg-August-Universität, Göttingen.

Start of project: 01.11.2014 - End of project: 30.11.2015

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
Metabolic Diseases and Nutrition

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 randomized 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_

Research Projects in Surgery

Assessment and training in minimally invasive surgery using virtual reality simulators:
Virtual reality (VR) simulation is increasingly used in surgical disciplines. Since VR simulators measure multiple outcomes, standardised reporting is needed. We present an algorithm for combining multiple VR outcomes into dimension summary measures, which are then integrated into a meaningful total score, and reanalyse the data of two VR studies applying the algorithm.
_Start of project: 24.04.2013 - End of project: 19.06.2015_

Definition and Classification of Intraoperative Complications (CLASSIC): Delphi Study and Pilot Evaluation:
This study aims at finding a system how to best capture and classify intraoperative complications in daily practice as well as in clinical studies for quality control in the perioperative settings. Whereas there are several validated systems for reporting postoperative complications, there are only a few and not prospectively validated systems for reporting intraoperative complications. We therefore develop a definition and classification for intraoperative complications within a Delphi study involving international interdisciplinary experts. The classification system will be retrospectively validated in a small pilot study.
_Start of project: 05.07.2012 - End of project: 10.02.2015_

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 is 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 shall show evidence whether or not intraoperative infiltration of local anesthetic have an impact on the development of chronic postoperative pain.
_Start of project: 14.03.2012 - End of project: 05.01.2015_

Residents’ performance in open versus laparoscopic bench-model cholecystectomy in a hands-on surgical course:
Laparoscopy has become the gold standard for many abdominal procedures. Among young surgeons, experience in laparoscopic surgery increasingly outweighs experience in open surgery. This study was conducted to compare trainees’ performance in open versus laparoscopic cholecystectomy in a cadaveric animal bench-model.
_Start of project: 05.09.2014 - End of project: 29.04.2015_
Oncology

**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 overall survival.

*Start of project: 06.01.2011 - End of project: 09.02.2015*

**[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 [177Lutetium-DOTA]-TOC. We will use Cox regression and competing risk regression models.

*Start of project: 01.01.2010 - End of project: 30.11.2015*

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*

Anesthesiology

**Succinylcholine: an observational study**
In this large observational study including over 1500 patients, we investigate predictors of the variability in neuromuscular block time following Succinylcholine considering clinical, biochemical and genetic factors. Succinylcholine is considered the neuromuscular blocking agent of choice for rapid sequence induction. Its short duration of action is potentially life saving by enabling the patient to regain spontaneous ventilation, should neither tracheal intubation nor mask ventilation be successful.

*Start of project: 23.12.2013 - End of project: 29.07.2015*
HIV Infection, Swiss HIV Cohort Study and Multicohort Projects

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: 30.06.2016

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. 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.

Optimising HIV-RNA monitoring in naıve 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 frequencing 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 optimisation 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: 30.06.2016

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 inhospital 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 inhospital 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.

* Project Leadership ± Project Partner
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: 31.10.2016

Tenofovir in HIV-infected patients pretreated with antiretroviral therapy: 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 tenofovir in HIV infected adults and children who are pretreated with an antiretroviral therapy (ART) and newly initiate Tenofovir treatment.
Start of project: 01.01.2013 - End of project: 31.05.2016

Methodological Research Projects

Comparative treatment effects of on-label and off-label drug use: 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.

Agreement of treatment effects for mortality from routinely collected data and subsequent randomised trials: meta-epidemiological survey*
We conduct an empirical evaluation of effects of various medical interventions for diverse conditions reported in routinely collected (health) data studies (RCD-studies) and RCTs. The agreement of treatment effects for mortality between these study types is evaluated based on RCD-studies using propensity scores for confounder control. We compare mortality effects reported in a systematically derived sample of RCD-studies, which were conducted prior to RCTs with effect sizes of subsequent RCTs addressing the same clinical question.
Start of project: 20.03.2013 - End of project: 31.01.2016

CEIT - Cancer (Comparative Effectiveness of Innovative Treatments for Cancer)*
Timely access to innovative treatments is paramount for patients with cancer. However, by applying flexibility to the approval pathways, substantial uncertainty in clinical decision-making is created, especially directly following approval. In this meta-epidemiological study, the approval studies for all 70 cancer treatments that were approved since the year 2000 will be systematically reviewed and their methods, size, and treatment effects evaluated. We will also evaluate the post-approval generation of clinical evidence on effects on overall survival, patient-important outcomes, and the most important cancer specific surrogate outcomes progression-free survival and tumor response. We will consider eligible randomised controlled trials (RCTs), systematic reviews and meta-analyses of such RCTs, and CER-studies (i.e. studies using observational data collected from routine patient care after approval, such as patient or disease registries, administrative databases or electronic health records). The ultimate goal is to provide decision-makers with guidance to identify early indications which innovative drugs likely fulfil the promise of therapeutic success in the long run and which should be used cautiously until more evidence is generated.
Start of project: 01.10.2015 - End of project: 01.01.2018
Concordance of treatment effects of “real world” observational studies 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.

Defining “Quality” in clinical research – A systematic review and structured framework*
The objectives of this study are 1) to systematically review suggested definitions for “quality” in the context of clinical research taking into consideration the viewpoints of different stakeholders; and 2) to develop a consistent and comprehensive framework of clinical research quality which could later serve as a basis to operationalise and develop a quality assessment/measurement tool of such.
Start of project: 01.10.2014 - End of project: 31.10.2017

Development and validation of an instrument to assess the credibility of putative subgroup effects in randomised controlled trials and meta-analyses*
The overall goal of this project is to provide clinicians, researchers, and decision-makers with a reliable, valid, and functional instrument for assessing the credibility of subgroup effects found in randomised trials and meta-analyses. In a first step, we will conduct a systematic survey of the methodological literature addressing the conduct and interpretation of subgroup analyses. We will identify and summarise currently suggested credibility criteria and the rationale offered for these criteria, in the process generating a list of potential instrument items and evidence or opinion about the relative merits of the criteria.
Start of project: 13.11.2013 - End of project: 30.04.2018

Epidemiology and publication of discontinued randomised trials, DISCO 1*

Randomised versus non-randomised discontinued studies, DISCO 1, subproject 4*
The objective of this study is to compare the prevalence and reasons for discontinuations between randomised controlled trials 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: 30.09.2016

Discontinuation of randomised controlled trials in pediatrics, DISCO 1, subprojects 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: 31.05.2016

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.


**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 RCT discontinuation due to poor recruitment, (ii) to examine to what extent and how investigators of RCTs discontinued 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 RCT 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: 31.05.2016

**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: 31.05.2016

**Design features DISCO 2, subproject 3***
This study is a matched comparison between discontinued 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: 30.09.2016

**Do routinely collected health data complement randomised evidence? A survey***
Observational studies using routinely collected data (RCD) may be important 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 are proposed to complement randomized controlled trials (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: 31.03.2016

**Effects of the Swiss human research legislation on the costs of randomised controlled trials**
The objectives of this study are to compile a comprehensive list of cost items for the planning and conduct of randomised controlled trials (RCTs) (industry and academic settings), to determine the unit costs for listed cost items and to evaluate the average/mean total cost of completed RCTs in
Switzerland, stratified by sponsor (industry vs. non-industry), and to compare the planning and preparation costs of RCTs in Switzerland before and after the introduction of the Swiss Legislation on Human Research in 2014

**Start of project: 01.07.2015 - End of project: 31.03.2017**

**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: 31.07.2017**

**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: 30.06.2016**

**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: 30.06.2016**

**HTA Reports**

**HTA report on bariatric surgery**

The aim of this HTA report for the Swiss Medical Board is to assess the effectiveness and safety as well as the economic, legal and ethical implications of bariatric surgery compared to conservative treatment, both in the population currently covered by Swiss obligatory health insurance (Obligatorische Krankenpflegeversicherung, OKP) (i.e. obese individuals with a BMI $\geq 35$ kg/m$^2$) and in patients currently not covered by the OKP (i.e. overweight or obese individuals with a BMI of 25 - 35 kg/m$^2$). While all the surgical interventions currently used were being considered, the main focus was gastric bypass. The CEB is responsible for the coordination of the project and the assessment of the effectiveness.

**Start of project: 01.06.2015 - End of project: 30.04.2016**
Infectious Diseases

Routine prescription feedback and peer comparison to lower antibiotic prescription in primary care: a pragmatic randomised controlled trial*
Excessive usage of antibiotics raises the emergence of resistant bacterias 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: 30.06.2016

Efficacy and safety of low-dose corticosteroids in patients with community acquired pneumonia: a 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: 30.09.2016

Cardiovascular and Lung Disease

Colchicine for prevention of cardiovascular events: a systematic review and meta-analysis*
Recently published results from randomised controlled trials indicate a potentially considerable benefit of low-dose colchicine treatment for prevention of cardiovascular events. In this project we systematically review and synthesise evidence on the effects of colchicine on cardiovascular outcomes.

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: 30.06.2016

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 disease.
Start of project: 01.01.2009 - End of project: 31.10.2016

Oncology

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.

**Intensive Care**

**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 polynoma interaction (MFPI) approach to investigate the interaction between continuous patient baseline characteristics (body mass index, PaO2/FiO2, 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: 31.05.2016

**Anesthesiology**

**CARBETOCIN trial - Carbtocin- Appropriate Rate Better Equilibrium between TOnus and CIrculatioN**

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

**PIEB – Programmed intermittent epidural bolus**

This retrospective cohort study aims at investigating the effects of Programmed intermittent epidural bolus (PIEB) combined with patient-controlled epidural bolus (PCEA) on maternal motor function and labour outcome in a typical trial patient (healthy nulliparous) as compared to non-trial patients (multiparous, non healthy women). The outcome will be analysed using general additive models (GAM).
Start of project: 11.02.2015 - End of project: 31.12.2017
**TEACHING**

**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 Master’s program at the University of Basel. Total teaching obligations in 2015 were 126 hours.

**Postgraduate**

University of Basel

1. H.C. Bucher. Öffentliche Gesundheit: Screening, Institute of Nursing Science, University of Basel, 20.05.2015 (6 hours).
2. M. Briel. Systematische Reviews und Meta-Analysen, Sponsor-Investigator Aufbaukurs 2015, Clinical Trial Unit, Departement Klinische Forschung, University Hospital Basel, 25.03.2015 and 09.09.2015 (1 hour each).
3. M. Briel, T. Fabbro, S. von Felten. Von der Forschungsfrage zur Studie, Sponsor-Investigator Aufbaukurs 2015, Clinical Trial Unit, Departement Klinische Forschung, University Hospital Basel, 25.03.2014 (1 hour).
5. M. Briel. Superiority and Non-inferiority Trials, Research Lunch 2015, University Hospital Basel, 19.05.2015 (1 hour).

Other academic institutions

1. H.C. Bucher, M. Briel. How to integrate results from indirect comparison and network meta-analysis into clinical decision making. Continuing education/Workshop, Deutsches EBM-Netzwerk, Berlin, 13.03.2015.
2. M. Briel. Introduction to evidence-based medicine. European Course in Tropical Epidemiology, Swiss Tropical and Public Health Institute, Basel, 27.08.2015 (2 hours).

**Supervision of Masters Theses**

1. R. Al Turki. 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. A. Ladanie. Faculty of Science, Epidemiology, supervised by H.C. Bucher and L.G. Hemkens.
Supervision of MD Theses

1. **A. Amstutz.** Empirical study on discontinuation and publication of SNF-supported randomised health care trials, supervised by **M. Briel**.
2. **T. Jakob.** Fibrates for primary prevention of cardiovascular disease events, supervised by **A. J. Nordmann** and **M. Briel**.
3. **M. Stegert.** An analysis of protocols and publications suggested that most discontinuations of clinical trials were not based on pre-planned interim analyses or stopping rules, supervised by **M. Briel**.

PhD Students (Epidemiology)

1. **M. Briel** MD, Epidemiology and determinants of randomized controlled trials discontinued for insufficient recruitment of participants, 2013-2016.
3. **A. Ladanie** MSc, Evolution of treatment effect evidence measured in randomized trials, 2015-2018.
4. **S. Nsanzimana** MD, Linkage to and Retention in HIV Care and Treatment in the Rwanda National HIV Programme: Optimizing the effectiveness for individual- and community-level outcomes in the era of pre-and on ART in Rwanda, 2015-2018.
# STAFF AS OF DECEMBER 31, 2015

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Employment</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>Rita Achermann, MSc</td>
<td>Biostatisticist</td>
<td>associated collaborator</td>
</tr>
<tr>
<td>Sonja Achermann, Business Economist</td>
<td>Controlling, Business Administrator</td>
<td>60%</td>
</tr>
<tr>
<td>Alain Amstutz, MSc</td>
<td>MD Candidate</td>
<td>40%</td>
</tr>
<tr>
<td>Assistant Prof. Matthias Briel, MD, MSc</td>
<td>Senior Scientist</td>
<td>associated collaborator</td>
</tr>
<tr>
<td>Prof. Annette Boehler, MD</td>
<td>Project Head</td>
<td>associated collaborator</td>
</tr>
<tr>
<td>Sanda Branca-Dragan, MSc</td>
<td>Biostatisticist</td>
<td>associated collaborator</td>
</tr>
<tr>
<td>Salome Dell-Kuster, MD, MSc</td>
<td>Biostatisticist</td>
<td>20%</td>
</tr>
<tr>
<td>Hannah Ewald, MPH</td>
<td>Research Associate, PhD Candidate</td>
<td>100%</td>
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<tr>
<td>Dominik Glinz, PhD</td>
<td>Research Associate</td>
<td>100%</td>
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<tr>
<td>Viktoria Gloy, PhD</td>
<td>Research Associate</td>
<td>40%</td>
</tr>
<tr>
<td>Lars Hemkens, MD, MPH</td>
<td>Senior Scientist</td>
<td>100%</td>
</tr>
<tr>
<td>Assistant Prof. Michael Koller, MD, MSc</td>
<td>Senior Scientist</td>
<td>associated collaborator</td>
</tr>
<tr>
<td>Aviv Ladanie, MSc</td>
<td>PhD Candidate</td>
<td>100%</td>
</tr>
<tr>
<td>Sandra Manz, BA</td>
<td>Administrative Assistant</td>
<td>40%</td>
</tr>
<tr>
<td>Tanja Manz</td>
<td>Administrative Assistant</td>
<td>40%</td>
</tr>
<tr>
<td>Prof. Alain Nordmann, MD, MSc</td>
<td>Senior Scientist, Assistant Professor</td>
<td>10%</td>
</tr>
<tr>
<td>Kübra Oezoglu, BSc</td>
<td>Student Aid</td>
<td></td>
</tr>
<tr>
<td>Heike Raatz, MD, MSc</td>
<td>Senior Scientist</td>
<td>100%</td>
</tr>
<tr>
<td>Selene Leon Reyes, PhD</td>
<td>Biostatisticist</td>
<td>100%</td>
</tr>
<tr>
<td>Juliane Rick, Biomathematician (FH)</td>
<td>Senior Data Manager</td>
<td>associated collaborator</td>
</tr>
<tr>
<td>Ramon Saccilotto, MD, MAS</td>
<td>Research Associate</td>
<td>associated collaborator</td>
</tr>
<tr>
<td>Juliane Schäfer, PhD</td>
<td>Biostatisticist</td>
<td>50%</td>
</tr>
<tr>
<td>Name</td>
<td>Position</td>
<td>Percentage</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>----------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Stefan Schandelmaier, MD</td>
<td>Research Associate</td>
<td>80%</td>
</tr>
<tr>
<td>Prof. Pedram Sendi, MD, DMD</td>
<td>Senior Scientist</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Assistant Professor</td>
<td></td>
</tr>
<tr>
<td>Susanne Stampf, PhD</td>
<td>Biostatistician</td>
<td></td>
</tr>
<tr>
<td></td>
<td>associated collaborator</td>
<td></td>
</tr>
<tr>
<td>Sarah Thommen, MSc</td>
<td>Junior Biostatistician</td>
<td>80%</td>
</tr>
<tr>
<td>Madeleine Wick, MS Pharm, MPH</td>
<td>Study Coordinator</td>
<td></td>
</tr>
<tr>
<td></td>
<td>associated collaborator</td>
<td></td>
</tr>
<tr>
<td>James Young, PhD</td>
<td>Senior Biostatistician</td>
<td>50%</td>
</tr>
</tbody>
</table>
2015 ANNUAL FINANCIAL STATEMENTS

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42 Balance Sheet as of December 31, 2015

43 Profit and Loss Account for the Fiscal Year from January 1, 2015 to December 31, 2015

44 Notes to the Annual Financial Statements
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 2015.

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

Ralph Maiocchi
Audit expert
Auditor in charge

Heribert Risterer
Audit expert

Basel, 27 May 2016
**BALANCE SHEET AS OF DECEMBER 31, 2015**

<table>
<thead>
<tr>
<th>Assets</th>
<th>December 31, 2015</th>
<th>December 31, 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed Assets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial Assets (cash and investments)</td>
<td>1’316’620.99</td>
<td>1’220’000.00</td>
</tr>
<tr>
<td>Total Fixed Assets</td>
<td>1’316’620.99</td>
<td>1’220’000.00</td>
</tr>
<tr>
<td><strong>TOTAL ASSETS</strong></td>
<td>1’316’620.99</td>
<td>1’220’000.00</td>
</tr>
</tbody>
</table>

| LIABILITIES AND EQUITY      |                   |                   |
| Current Liabilities         |                   |                   |
| Deferred income             | 10’000.00         | 0.00              |
| Accrued liabilities         | 0.00              | 30’000.00         |
| Total Liabilities           | 10’000.00         | 30’000.00         |

| Endowment Fund              |                   |                   |
| Endowment capital           | 150’000.00        | 150’000.00        |
| Contributions from Bangerter-Stiftung | 1’020’000.00 | 1’020’000.00 |
| Profit carried forward      | 20’000.00         | 0.00              |
| Net Income 2015             | 116’620.99        | 20’000.00         |
| Total Endowment Fund of the Foundation | 1’306’620.99 | 1’190’000.00 |
| **TOTAL LIABILITIES AND EQUITY** | 1’316’620.99 | 1’220’000.00 |
# Profit and Loss Account for the Fiscal Year from January 1, 2015 to December 31, 2015

<table>
<thead>
<tr>
<th>Category</th>
<th>2015 (CHF)</th>
<th>2014 (CHF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contributions</td>
<td>0.00</td>
<td>20'000.00</td>
</tr>
<tr>
<td>Other income</td>
<td>0.00</td>
<td>6'350.00</td>
</tr>
<tr>
<td>Extraordinary income</td>
<td>30'000.00</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Total Operating Profit</strong></td>
<td><strong>30'000.00</strong></td>
<td><strong>26'350.00</strong></td>
</tr>
<tr>
<td>Administration and consulting</td>
<td>-6'132.00</td>
<td>-6'350.00</td>
</tr>
<tr>
<td>Advertising and public relations</td>
<td>-13'639.22</td>
<td>0.00</td>
</tr>
<tr>
<td>Other operating charges</td>
<td>-12'877.88</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Operating Loss/Profit</strong></td>
<td><strong>-2'649.10</strong></td>
<td><strong>20'000.00</strong></td>
</tr>
<tr>
<td>Financial income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Interest earned</td>
<td>11.53</td>
<td>0.00</td>
</tr>
<tr>
<td>- Income from value fluctuation reserve</td>
<td>119'258.56</td>
<td>0.00</td>
</tr>
<tr>
<td>Financial expenses</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>NET INCOME FOR THE YEAR</strong></td>
<td><strong>116'620.99</strong></td>
<td><strong>20'000.00</strong></td>
</tr>
</tbody>
</table>
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 as of December 31st, 2015
R. Guetg MD, President
Prof. J. D. Leuppi MD PhD, Member
lic.rer.pol. S. Kaufmann, Member

Two members of the Board of Trustees are authorised to sign collectively on behalf of the Foundation. The term of office for the members is three years, re-election being allowed.

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, Member of the Board of Directors of the University Hospital Basel
Prof. A. Knottnerus MD, University of Maastricht, The Netherlands
Prof. A. Detsky MD, University of Toronto, Canada

Director (Head of Institute)
Prof. H. C. Bucher MD MPH with authorisation to sign alone on behalf of the Foundation.

External Auditors
PricewaterhouseCoopers AG, Basel

Personnel
The Foundation does not employ any personnel.
1.4 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 2013 and the Annual Report 2013 have been accepted by way of a disposition dd. November 3rd, 2015. The disposition contained no remark at all. The Financial Statements 2014 and the Annual Report 2014 have been filed with the Basel Supervisory Authority in good time. At the time of printing of the 2015 Annual Report 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 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.

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. This also includes donations, legacies and other contributions in favour of the Foundation.

On August 21st, 2015 total funds in the amount of CHF 1’220’000.00 as shown in the 2014 Financial Statements together with CHF 119’258.56 being the pro rata Value Fluctuation Reserve (“Schwan-kungsreserve”) from the general Third Party's Fund of the University Hospital of Basel (“Dritt-mittelfonds des Universitätsspital Basel”) had been transferred to Basellandschaftliche Kantonalbank and credited to an account of the Foundation. The investment of the Foundation’s assets will be made in accordance with the investment regulations as approved by the Board of Trustees on November 20, 2015.

As of December 31st, 2015 100% of the Foundation’s assets have been invested in the investment category “Money Market Instruments and Cash”.

2.2 Further Explanations
The new requirements in force regarding bookkeeping and accounting according to Swiss Code of Obligations (Article 957 et seq.) have been taken into account for the preparation of the Financial Statements 2015. The Financial Statements 2014 have been adjusted accordingly.

The amount of CHF 10’000.00 as shown in „Deferred Income“ includes the costs for auditing of the Financial Statements 2015 (auditing company and Basel Supervisory Authority) payable in 2016 and the costs for producing the Annual Report 2015.

2.3 Notes to the Investment of Assets in accordance with the Foundation’s Investment Regulations
The assets must be managed accordingly in a manner which ensures security and sufficient income, an adequate risk distribution and the need to cover foreseeable liquidity requirements.
The Investment Committee consists of two members of the Board of Trustees. The investment strategy is determined and from time to time reviewed by the Board of Trustees. Such Board is also responsible for the management of the assets. Longterm investment goals and the distribution of assets in the various investment categories in compliance with maximum and minimum limits are defined by the investment strategy:

<table>
<thead>
<tr>
<th>Investment Category</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Money Market Instruments, Cash</td>
<td>10%</td>
<td>100%</td>
<td>15%</td>
</tr>
<tr>
<td>Bonds CHF</td>
<td>0%</td>
<td>70%</td>
<td>45%</td>
</tr>
<tr>
<td>Swiss Stocks</td>
<td>0%</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>International Stocks (without Swiss Stocks)</td>
<td>0%</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Real Estate in Switzerland</td>
<td>0%</td>
<td>10%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Apart from investments in bank account and time deposits the Investment Regulations provide for investments in money market instruments of first rate domestic debtors.

In case of investments in tradeable bonds (CHF) a minimum rating of AA and Aa2 (S&P and Moody’s, respectively) must be retained. Investments in shares of listed companies with a rating of AAA are allowed. In addition, investments in equity-like securities like non-voting equity securities (Genussscheine) and participation certificates or in corresponding collective investment schemes are possible. Investments in collective investment schemes are allowed (real estate fund and real estate company) whereas direct investments in real estate are not allowed. The use of derivatives und structured products is prohibited.

The Investment Regulations specify the following valuation principles:

<table>
<thead>
<tr>
<th>Investment Category</th>
<th>Valuation Principle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Money Market Instruments/Cash</td>
<td>at market value = par</td>
</tr>
<tr>
<td>2. Bonds</td>
<td>at market value = list price</td>
</tr>
<tr>
<td>3. Stocks</td>
<td>at market value = list price</td>
</tr>
<tr>
<td>4. Real Estate</td>
<td>at market value = list price</td>
</tr>
</tbody>
</table>

Until December 31\textsuperscript{st}, 2014, investments of assets have been handled on a fiduciary basis centrally by the Third Party’s Fund of the University Hospital of Basel.