EVIDENCE FOR DECISION MAKING IN HEALTH CARE
ANNUAL REPORT 2016
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34 Staff as of December 31, 2016
Dear reader

What is special about the Basel Institute for Clinical Epidemiology and Biostatistics (CEB)? It is a relatively small institute with minimal funding from the University with an enormous research output for its size. But it is not only the sheer number of publications it’s the quality and the impact of research results which is changing clinical research and patient management.

Let me just highlight one publication in this report that attracted my attention. Researchers from CEB conducted a pragmatic trial using claim data to investigate whether routine monitoring and feedback to high prescribers of antibiotics can reduce antibiotic prescriptions in primary care. While the results are slightly disappointing I felt the approach to conduct a nationwide intervention trial that is based on routinely collected data fascinating and very innovative.

How can such quality be achieved? I think it is mainly the merit of the entire team, the openness to explore new ideas and the knowledge, dedication and persistence of the senior researchers assisting juniors in pursuing their projects and academic careers. An excellent national and international research network and the drive for excellence are the additional ingredients for this success.

CEB is an associated institute of the University of Basel and would not be possible without the funds from its foundation ‘Stiftung Institut für Klinische Epidemiologie’. The concern of the board of trustees is how to maintain the output of CEB in an increasingly difficult academic environment where funds are getting scarce. 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 another year with an outstanding performance in research and teaching and to 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
Stefan Kaufmann lic. rer. pol., Prof. Jörg D. Leuppi MD, PhD, Reto Guet MD

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OUR MISSION IS TO IMPROVE DECISION MAKING IN HEALTH CARE

Our goal is evidence-based health care. We investigate whether new or established technologies in medicine improve patient relevant outcomes. We generate and appraise evidence of medical interventions by our research and evidence synthesis. We use different techniques to document how new interventions perform in a real world setting by using large cohorts, routinely collected data and registries. We develop and teach the methods of evidence based medicine to improve the quality of clinical research.

OUR STRATEGY

CEB has an explicit focus on translational health research to investigate how patients gain timely access to new technologies with clinically relevant benefits. We evaluate the comparative effectiveness of new interventions and technologies when used in the real world setting and examine whether new products are safe and represent added value to health care systems.

OUR PRINCIPLES

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 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, individual patient data and network meta-analyses, standard meta-analyses, Health Technology Assessments and methodological support for clinical researchers, governmental agencies, health insurers, and industry.
The team of CEB
RESEARCH HIGHLIGHTS OF CEB IN 2016

Chronic Hepatitis B and C virus infection and risk for non-Hodgkin lymphoma in HIV-infected patients: A cohort study.

**Background:** Non-Hodgkin lymphoma (NHL) is the most common AIDS-defining condition in the era of antiretroviral therapy (ART). We investigated whether chronic hepatitis B (HBV) and hepatitis C infection (HCV) are associated with increased incidence of NHL in HIV-infected patients.

**Methods and Results:** We analysed 52,479 treatment-naive patients (1339 [2.6%] with chronic HBV infection and 7506 with chronic HCV infection [14.3%]) from 18 of 33 cohorts from the Collaboration of Observational HIV Epidemiological Research Europe (COHERE). Of those, 40,219 (77%) patients later started ART. A total of 252 treatment-naive patients and 310 treated patients developed NHL, with incidence rates of 219 and 168 cases per 100,000 person-years, respectively. The hazard ratios for NHL with HBV and HCV infection were 1.33 (95% CI, 0.69 to 2.56) and 0.67 (CI, 0.40 to 1.12), respectively, in treatment-naive patients and 1.74 (CI, 1.08 to 2.82) and 1.73 (CI, 1.21 to 2.46), respectively, in ART treated patients.

**Conclusions and Relevance:** In HIV-infected patients receiving ART, chronic co-infection with HBV and HCV is associated with an increased risk for NHL.

Agreement between industry and academia on publication rights: A retrospective study of protocols and publications of randomized controlled trials.

**Background:** Little is known about publication agreements between industry and academic investigators in trial protocols and the consistency of these agreements with corresponding statements in publications.

**Methods and Results:** We investigated the documentation of publication agreements in archived randomised controlled trial protocols approved by six research ethics committees between 2000 and 2003 and statements in corresponding journal publications. Of 647 eligible randomized control trial (RCT) protocols, 70.5% mentioned an agreement regarding publication of results, 86.2% documented an industry partner’s right to disapprove or review manuscripts, and 8.6% contained no constraints of publication. Most agreements documented in the protocol were not reported in the subsequent publication (197/268 [73.5%]). Of 71 agreements reported in publications, 52 (73.2%) were concordant with those documented in the protocol.

**Conclusions and Relevance:** Publication agreements constraining academic authors’ independence are common but seldom reported and if reported can be discrepant with the trial protocols.

Personalized prescription feedback using routinely collected data to reduce antibiotic use in primary care: A randomized clinical trial.

**Background:** Feedback interventions using routinely collected health data might reduce antibiotic use nationwide without requiring the substantial resources and structural efforts of other antibiotic stewardship programs.

**Methods and results:** In a pragmatic randomized trial using routinely collected claims data on 2900 primary care physicians with the highest antibiotic prescription rates in Switzerland we investigated if quarterly antibiotic prescription feedback over 2 years reduces antibiotic use. Feedback was provided both by mail and online from October 2013 to October 2015 and was supported by an initial one time provision of evidence-based guidelines. The 2900 physicians had 10,660,124 consultations over 2 years of follow-up, prescribed 1,175,780 packages of antibiotics with 10,290,182 defined daily doses (DDD). Physicians receiving feedback prescribed the same amount of antibiotics to all patients in the first year (between-group difference, 0.81%; 95% CI, -2.56% to 4.30%; P = .64) and second year (between-group difference, -1.73%; 95% CI, -5.07% to 1.72%; P = .32) compared with the control group. Prescribing to children aged 6 to 18 years was -8.61% lower in the feedback than in the control group in the first year (95% CI, -14.87% to -1.90%; P = .01). This difference diminished in the second year (between-group difference, -4.10%; 95% CI, -10.78% to 3.07%; P = .25). Physicians receiving feedback prescribed fewer antibiotics to adults aged 19 to 65 years in the second year (between-group difference, -4.59%; 95% CI, -7.91% to -1.16%; P < .01). Prescribing to other patient groups or of specific antibiotic types was not significantly different between groups.

**Conclusions and Relevance:** This nationwide antibiotic stewardship program with routine feedback on antibiotic prescribing was not associated with a change of antibiotic use. In older children, adolescents, and younger adults less antibiotics were prescribed, but not consistently over the entire intervention period.
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

<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>36</td>
<td>2.6</td>
<td>35.72</td>
</tr>
<tr>
<td>Prof. H.C. Bucher</td>
<td>52</td>
<td>2.9</td>
<td>33.23</td>
</tr>
<tr>
<td>PD Dr. Michael Koller</td>
<td>27</td>
<td>2.1</td>
<td>12.12</td>
</tr>
<tr>
<td>Prof. A. Nordmann</td>
<td>23</td>
<td>1.8</td>
<td>28.03</td>
</tr>
</tbody>
</table>

\(^1\) 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 11 years.

![Citation frequency and number of indexed publications of senior researchers of CEB from 2001 to 2016 (Thompson Science Citation Index)](chart.png)
CEB RESEARCH

In 2016 CEB has published 49 publications in peer reviewed journals, some of them in prestigious journals like JAMA; British Medical Journal, Annals of Internal Medicine, JAMA Internal Medicine or Plos Medicine.

This year’s publications highlight our strength in methodological research. A total of 14 publications (3, 5, 7, 8, 18, 19, 21, 26, 27, 30, 38, 42, 43, 44) dealt with methodological issues covering bias in dissemination of clinical research findings (3), providing guidance for the reporting of routinely collected data (5, 19, 27), detailing reasons for discontinuation of clinical trials (7, 8, 38, 42, 44), examining the consistency of reporting of industry support and independence for reporting of study findings in research protocols and subsequent publications in clinical (30) and illucidating the quality of life reporting in cancer trials (43). Further publications examined the consistency and quality of research results reported in observational and randomised controlled trials investigating the same research question (18, 21, 26).

Our long-lasting expertise in systematic reviews is reflected by 10 publications on pneumococcal conjugate vaccines (14), antiretroviral drug treatment with tenofovir in treatment experienced HIV-infected patients (15), nutrition support in malnourished hospitalised patients (4), colchicine for the prevention of cardiovascular events (20, 22, 23), fibrates for primary prevention of cardiovascular disease events (29), lymph node yield after rectal resection in patients treated with neoadjuvant radiation for rectal cancer (36), early statin therapy in acute coronary syndromes (37) and on the effects of bariatric surgery on mortality, cardiovascular events, and cancer outcomes in obese patients (49).

We published two randomised controlled trials on the effectiveness of routine monitoring and feedback to reduce antibiotic prescriptions in primary care physicians in Switzerland (24, 25) and on the efficacy and safety of carbetocin applied as an intravenous bolus compared to as a short-infusion for caesarean section (13).

Four publications relate to our international collaboration in observational data analyses in HIV (11, 12, 47, 48). In a project from the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) we could show, that chronic hepatitis B and C infections are associated with an increased risk of non-Hodgkin lymphoma (48). Two publications from collaborations with the Harvard School of Public Health investigated the swichting and monitoring strategies of HIV infected patients receiving antiretroviral therapy (11, 12). Three publications from our Rwandan PhD student deal with the problems of accelerating the initiation of antiretroviral therapy and improving the continuum of care for HIV infected patients in resource limited settings (6, 17, 37).

\(^1\) Number refers to the list of publications (see section “Publications of CEB in 2016”).
Team of Biostatisticians
Dr. Giusi Moffa, Dr. James Young, Dr. Salome Dell-Kuster, Dr. Soheila Aghlmandi

Clinical Epidemiology & Methodology Team
Hannah Ewald, Kübra Oezoglu, Dr. Benjamin J. Speich, PD Dr. Matthias Briel, Aviv Ladanie, Dr. Lars G. Hemkens, Kimberly McCord, Dmitry Gryaznov, Prof. Heiner C. Bucher (Prof. Alain Nordmann, 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 masters program at the University of Basel. Total undergraduate teaching obligations in 2016 were 126 hours. We have increased our teaching activities in postgraduate education in research methodology. Collaborators of the institute participate in post-graduate clinical investigator courses. In 2016 CEB was training 6 PhD students and 6 Master students. PhD students have been involved in 8 publications (6, 14, 15, 17, 20, 22, 23, 37) and first authors in 2 publications (14, 15).

CEB CONSULTING

CEB is providing consultancy services to the Department Clinical Research and Surgery at the University Hospital Basel. Services include clinical epidemiological and analytical support. Two publications (28, 46) originated from this collaboration.

Health Technology Assessment (HTA)

CEB is commissioned by the Swiss Medical Board for conducting HTA reports in Switzerland and leads a consortium that involves the European Center for Pharmaceutical Medicine, University of Basel, the Epidemiology, Biostatistics and Prevention Institute, University of Zurich, and the Institute Ethic Histoire Humanité, University of Geneva. We have finished the report on bariatric surgery vs. conservative treatment for obesity and overweight.

CEB has consultancy mandates for Health Technology Assessments from the Swiss Federal Office of Public Health. 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 (S-CORE) involving researchers from the Faculty of Medicine, the Faculty of Business and Economics and the Faculty of Science at the University of Basel.
**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 2016 the study has included 4023 solid organ transplanted patients. There are more than 100 ongoing research projects and 12 studies have been published in 2016, with 3 studies (4, 32, 33) where collaborators of the data center are co-authors (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.
2016 was an extremely productive year with a high number of publications in prestigious journals, acquisitions of new grants and HTA projects. I would like to thank my team for these fantastic achievements. It is a privilege, fun and very stimulating to lead such a great team.

Prof. Heiner C. Bucher MD MPH
Director of the Institute
Original Publications in Peer Reviewed Journals


(31) Kasenda B., Sauerbrei W., Royston P., Mercat A., Slutsky A.S., Cook D., Guyatt G.H., Brochard L., Richard J.C., Stewart T.E., Meade M., Briel M. Multivariable fractional polynomial interaction to investigate continuous effect modifiers in a meta-analysis on higher versus lower PEEP for patients with ARDS. *BMJ Open* 2016 Sep 8; 6(9):e011148. doi: 10.1136/bmjopen-2016-011148.


Research Letters, Letters and Non-Peer Reviewed Publications


Reports


Presentations


(9) Briel M. Discontinuation and non-publication of randomized clinical trials supported by the Swiss National Science Foundation. Swiss National Research Council, Berne: December 6, 2016.


(13) Dell-Kuster S. Efficacy and safety of intravenous carbetocin as a bolus compared to a short infusion for caesarean section. Obstetric Anaesthesia 2016 Meeting, Manchester, UK: May 19, 2016.


Posters and Abstracts


(6) Leu S., Boulay J.L., Thommen S., Bucher H.C., Stippich C.H., Mariani L., Bink A. Impact of the volumes of different tumor components in glioblastoma on overall survival. 21st Annual Scientific Meeting and Education Day of the Society for Neuro-Oncology, Scottsdale, USA: November 18, 2016.


ACCOMPLISHED PROJECTS IN 2016

HIV Infection, Swiss HIV Cohort Study and Multicohort Projects

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 has served 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. Funding from the EU for this project has ended in 2015.

Tenofovir in HIV-infected patients pretreated with antiretroviral therapy: A systematic review and meta-analysis of randomized 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 treatment with tenofovir.

Prevalence of physical activity in patients with HIV over time: The Swiss HIV Cohort Study
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.

Utilisation and effectiveness of daclatasvir-based treatment regimes in chronic hepatitis C infection in Europe – real-world data from named patient programs in Europe
Daclatasvir (DCV) is a new, direct-acting antiviral agent for the treatment of chronic hepatitis C virus infection. It received marketing authorization from the European Medicines Agency in August 2014 under an accelerated-review process on the basis of single-arm, phase II trial results. Using European data from patients included in a ‘Named Patient Program’ and from the early post-marketing authorization period, this study will describe patient characteristics and effectiveness of DCV-based regimens in Europe prescribed outside of clinical trials. This project is funded by Bristol-Myers Squibb.

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 populations. 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: 31.10.2016
Methodological Research Projects

Agreement of treatment effects for mortality from routinely collected data and subsequent randomized 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 randomized controlled trials (RCT). 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.

Stopped trials early for benefit – trials published after a stopped trial – ethical? (STOP-IT 3)*
The study investigates how often randomised 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 a 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.

Do routinely collected health data complement randomized 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 (RCT) 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. 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

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

Epidemiology and publication of discontinued randomised trials; DISCO 1

DISCO – Pediatrics DISCO 1*
The objective of this study is to determine the prevalence of, and reasons for, discontinuation of randomized controlled trials (RCT) 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
DISCO – Randomised versus non-randomised discontinued studies, DISCO 1*
The objective of this study is to compare the prevalence and reasons for discontinuations between randomized controlled trials and non-randomized 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

Learning from failure – Understanding the mechanisms of trial discontinuation DISCO 2*
In a first project we will conduct semi-structured interviews with principal investigators of 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 SNSF 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.

DISCO – design features DISCO 2*
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.

DISCO – Registered discontinued RCTs DISCO 2*
The objective of this project is to examine the accuracy of completion status and reasons for discontinuation documented in trial registries and to investigate potential predictors for accurate trial status information in registries. In order to achieve this we will compare published reports from discontinued RCTs (reference standard) to information documented in registries for the same trials.

DISCO – Reporting of discontinued trials DISCO 2*
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.

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 the obligatorische Kranken- und Pflegeversicherung (OKP) (i.e. obese individuals with a BMI ≥35 kg/m²) and in patients currently not covered by the OKP (i.e. overweight or obese individuals with a BMI of 25 - 35 kg/m²). While all the surgical interventions currently used were being considered, the main focus was gastric bypass.

**Start of project: 01.06.2015 – End of project: 30.04.2016**

### Infectious Diseases

**Efficacy and safety of low-dose corticosteroids in patients with community acquired pneumonia (CAP): Systematic review and individual patient-data meta-analysis (IPD) of randomized trials (RCT)**

We will undertake a systematic review and IPD meta-analysis of all available RCTs to study the benefits and possible harms of using adjunctive low-dose corticosteroids in the treatment of patients with 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**

**Personalized prescription feedback to reduce antibiotic overuse in primary care: nationwide pragmatic randomized 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: 31.12.2016**

### Cardiovascular and Lung Disease

**Colchicine for prevention of cardiovascular events: systematic review and meta-analysis**

Recently published results from randomized controlled trials indicate a potentially considerable benefit of low-dose colchicine treatment for prevention of cardiovascular events. 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: 29.02.2016**

**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: 31.12.2016**

### 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 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 and surgery

**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: 31.07.2016* 

Reversal after Hartmann's procedure in patients with complicated sigmoid diverticulitis

Hartmann’s procedure (HP) is commonly used for the emergency treatment of complicated sigmoid diverticulitis (CSD). While it is intended to restore intestinal continuity, in practice reversal is not carried out in all cases. It is important to know the frequency of reversal and the impact of patient-related factors on the decision for reversal. We therefore conduct a retrospective on all patients who underwent HP for CSD at a tertiary referral hospital between May 2005 and December 2010 and assess the frequency of reversal over time and the prognostic factors affecting the decision for reversal.

*Start of project: 09.01.2013 – End of project: 02.11.2016* 

Anesthesiology

**Carbetocin study: Carbetocin – 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.

*Start of project: 02.01.2012 – End of project: 31.12.2016*
HIV Infection, Swiss HIV Cohort Study and Multicohort Projects

**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 in-hospital 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 in-hospital 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: 31.06.2017*

**Optimizing HIV-RNA monitoring in naïve patients initiating ART***

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 frequency 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: 31.03.2017*

**Impact of non-standardized outcome analyses on clinical care of HIV patients: Meta-epidemiological study***

There is no standard approach to deal with treatment switches or missing outcome data in HIV clinical trials, but this happens in up to 30% of patients in such trials. Many of the most commonly applied approaches may lead to biased results and may cause misleading clinical decision making. We conduct a meta-epidemiological study evaluating a large number of recent trials aiming to provide healthcare decision makers with an empirical estimate of the impact of analyses on clinical care by describing how frequently using a different approach would change the clinical interpretation of trial results.

*Start of project: 01.02.2016 – End of project: 31.01.2017*

**Smartphone app and CO self-monitoring for smoking cessation: A randomised controlled trial nested into the Swiss HIV Cohort Study***

This a randomized controlled trial nested in the Swiss HIV cohort is comparing the effectiveness of a smartphone app and carbon monoxide self-monitoring support for smoking cessation. The primary outcome is the combination of self-reported continuous abstinence biochemically verified by a carbon monoxide test in-person, with a cut-off of 7 ppm, at 6 months.

*Start of project: 09.08.2016 – End of project: 30.06.2018*

**ART-CC Single Tablet***

Most patients with HIV start antiretroviral therapy on a single tablet once a day regimen. However it is not clear whether single tablet regimens actually lead to better clinical outcomes. The best way to estimate the effect of reducing the pill burden of antiretroviral therapy is to compare single tablet regimens with multiple tablet regimens where all regimens contain the same drugs. We will
investigate whether Atripla®, the first single tablet regimen, is non-inferior for both virological failure and progression to AIDS or death relative to two or three pill formulations of the same regimen. Using off-patent drugs in multiple tablet regimens instead of adding these drugs to more expensive single tablet regimens could lead to important cost savings.

Start of project: 01.04.2014 – End of project: 30.06.2017

Methodological Research Projects

**Pragmatic randomized trials using routinely collected health data: Meta-epidemiological study**

Large and simple pragmatic trials may be conducted with only a fraction of costs of traditional trials when they use routinely collected health data (RCD) such as electronic health records or administrative claims data to assess outcomes. Various errors and biases of RCD may reduce their reliability. The relevance of this and many other limitations or advantages are unknown. We conduct the first systematic empirical analysis of RCTs using RCD for outcome assessment. We describe the current research agenda in this novel field and estimate the ability of RCD trials to measure outcomes as accurately as traditional randomized trials.

Start of project: 01.02.2016 – End of project: 31.01.2017

**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 operationalize 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 randomized 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 randomized 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 summarize 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

**Effects of the Swiss human research legislation on the costs of randomised controlled trials (RCT)**

The objectives of this study are to compile a comprehensive list of cost items for the planning and conduct of 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 & HFG and thereafter. In addition, we will evaluate the extent of appropriately registered protocols before the introduction of SPIRIT & HFG and thereafter (in national or international registries).

Start of project: 07.11.2014 – End of project: 31.07.2017

CEIT – Cancer (Comparative Effectiveness of Innovative Treatments for Cancer) *

Timely access to innovative treatments is paramount for patients with cancer. This meta-epidemiological study systematically evaluates the approval studies for over 70 new cancer treatments approved since 2000 and the post-approval generation of evidence on their effects on patient-important outcomes and cancer specific surrogate outcomes. The ultimate goal is to provide decision-makers with guidance to identify early indications on which innovative drugs likely fulfill 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: 30.06.2018

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.


Concordance of treatment effects of “real world“ observational studies using marginal structural models and randomized controlled trials: 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: 31.04.2017
Infectious Diseases

Routine antibiotic prescription feedback and resistance monitoring in primary care physicians: a nationwide pragmatic randomized trial (NFP 72)*
Antibiotic resistance is a serious public health threat which is amplified by antibiotic consumption in the population. We will conduct a nationwide pragmatic randomized trial on antibiotic prescription feedback and resistance monitoring in primary care physicians that uses routinely collected individual anonymized claim data to minimize antibiotic overuse and unnecessary use of broad spectrum antibiotics in primary care in Switzerland. In a feasibility sub-study, we will link insurance data with national antibiotic resistance data (Anresis) by anonymized privacy preserving probabilistic record linkage to study the impact of the intervention on antibiotic resistance.
Start of project: 01.01.2017 – End of project: 31.12.2019

Antivirals for influenza like syndrome: A randomised controlled trial of clinical and cost effectiveness in primary care±
Influenza is a highly contagious infection with considerable morbidity, mortality in particular in the elderly and economic implications. Therefore individuals at high risk from influenza related complications and health care staff should be annually vaccinated. Whether antiviral treatment of patients with flu-like syndroms during influenza seasons is beneficial remains controversial. In this large trial 4500 children and adults from 20 European networks will be randomized to oseltamivir, nitazoxanide (each for 5 days), or usual care. Outcomes of interest are return to normal daily activity and the cost-effectiveness of the interventions. The trial represents work package 4 of the Platform of European Preparedness against Reemerging Epidemics (PREPARE) and is funded by the EU, with CEB representing the Swiss network.
Start of project: 01.10.2015 – End of project: 30.09.2017

Anesthesiology

Programmed intermittent epidural bolus technique: external validity of trial results*
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).

International multicentre validation study of CLASSIC – Classification of Intraoperative Complications*
Quantifiable evidence-based methods for reporting complications are needed to improve perioperative patient safety. While there are several validated systems for reporting postoperative complications, there are only a few for reporting intraoperative complications. Our group developed a definition and classification for intraoperative complications within a Delphi study involving international interdisciplinary experts. All patient-related intraoperative complications from surgery or anaesthesia are considered. This current cohort study aims to assess the validity and feasibility of this newly derived classification in an international multicentre cohort study. Providing a well-applicable internationally validated classification system for intraoperative complications is an important contribution to the quality of health care and perioperative patient safety.
Start of project: 01.01.2015 – End of project: 01.01.2019
Undergraduate

University of Basel

H.C. Bucher, M. Briel, L.G. Hemkens, H. Raatz 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 Basel. Total teaching obligations in 2016 were 126 hours.

Postgraduate


Supervision of Master Theses

1. Armon Arpagaus. Faculty of Medicine, University of Basel. Colchicine and niacin in cardiovascular diseases supervised by M. Briel and L.G. Hemkens.
2. Roy Frei. Faculty of Medicine, University of Basel. Empiric research on discontinuation and registration of randomized clinical trials supervised by M. Briel.
3. Dmitry Gryaznov. Faculty of Science, Epidemiology, University of Basel. Comparison of prevalence and characteristics of patient reported outcomes in protocols of randomized trials from 2000-3 and 2012 – an empirical study supervised by M. Briel.
5. Jakub Surina. Faculty of Science, Bioinformatics. University of Tübingen. Discontinuation and publication of health care randomized controlled trials supported by the Swiss National Science Foundation supervised by M. Briel.
Supervision of MD Theses


PhD Students (Epidemiology)

1. Matthias Briel. MD. Epidemiology and determinants of randomized controlled trials discontinued for insufficient recruitment of participants, 2013-2016.
4. Sabin Nsanzimana. MD, MSc. 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.
<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
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<tbody>
<tr>
<td>Prof. Dr. med. Heiner C. Bucher, MPH</td>
<td>Head of Institute</td>
<td>100%</td>
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<tr>
<td>Rita Achermann, MSc</td>
<td>Biostatistician</td>
<td>associated collaborator</td>
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<tr>
<td>Serena Bianco-Scudella</td>
<td>Research Fellow</td>
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<tr>
<td>PD Dr. med. Matthias Briel, MSc</td>
<td>Senior Scientist</td>
<td>associated collaborator</td>
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<tr>
<td>Prof. Dr. med. Annette Boehler</td>
<td>Project Head</td>
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<tr>
<td>Sanda Branca</td>
<td>Statistician</td>
<td>associated collaborator</td>
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<tr>
<td>Dr. med. Salome Dell-Kuster, MSc</td>
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<tr>
<td>Hannah Ewald, MPH</td>
<td>PhD Student Epidemiology</td>
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<td>Dr. sc. Dominik Glinz, MSc PhD</td>
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<tr>
<td>Dr. sc. Viktoria Gloy, MSc PhD</td>
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<td>Dr. med. Lars Hemkens, MPH</td>
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<td>PD Dr. med. Michael Koller, MSc</td>
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<tr>
<td>Aviv Ladanie, MSc</td>
<td>PhD Student Epidemiology</td>
<td>100%</td>
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<tr>
<td>Selene Leon Reyes, PhD</td>
<td>Biostatistician</td>
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<tr>
<td>Sandra Manz, BA</td>
<td>Administrative Assistant</td>
<td>80%</td>
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<tr>
<td>Kimberly Mc Cord, BSc</td>
<td>Student Aid</td>
<td>30%</td>
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<td>Prof. Dr. med. Alain Nordmann, MSc</td>
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<td>Kübra Oezoglu, BSc</td>
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<td>Dr. med. Heike Raatz, MSc</td>
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<td>Juliane Rick, Dipl. Biomathematikerin (FH)</td>
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<td>Dr. med. Ramon Saccilotto</td>
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<td>Madeleine Wick, Dipl. Pharm. MPH</td>
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<tr>
<td>Dr. Jim Young, PhD</td>
<td>Senior Biostatistician</td>
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