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<td>Staff as of December 31, 2017</td>
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Dear reader

The board of trustees of the foundation is proud to present you the annual report 2017. It has been a particular successful year for the Basel Institute for Clinical Epidemiology and Biostatistics (CEB).

We are impressed by the output and quality of this relatively small institute with minimal funding from the University. We are particularly satisfied by the multitude of publications in different areas, which reflect the remarkable network of established collaborations. There is an increasing number of publications that results from consultancy for the University Hospital Basel and the Department of Clinical Research.

We are proud that three senior researchers of CEB received this year the venia docendi (assistant professorship) at the University of Basel. The continuous support of the director of CEB and financial support from the Stiftung Institut für Klinische Epidemiologie have made these achievements possible. CEB has also gained additional reputation in its methodological research during this year. This is reflected in large number of publications that deal all with methodological issues that aim at improving clinical research methodology and reducing the publication of biased research results.

The achievements of the team of CEB are outstanding and receive our full respect and support. My thanks go to a team of outstanding researchers, the director Professor Bucher and the clinical research manager Diana Grauwiler for providing an excellent research environment and leadership.

Reto Guetg MD
President of the Board of Trustees
Foundation Institute for Clinical Epidemiology
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 performed in a real world setting by using large cohorts, routine 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 a real world setting and examine whether new products 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

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.
RESEARCH HIGHLIGHTS OF CEB IN 2017

Off-label treatments were not consistently better or worse than approved drug treatments in randomized trials. Ladanie A et al. *J Clin Epidemiol* 2017 Nov 13. Epub [ahead of print]

**Background:** Off-label drug use is highly prevalent but controversial and often discouraged assuming generally inferior medical effects associated with off-label use.

**Methods and Results:** We searched the literature for meta-analyses of randomized clinical trials (RCTs) comparing off-label and approved drugs head-to-head in any population and on any medical outcome. We combined the comparative effects in meta-analyses providing summary odds ratios (sOR) for each treatment comparison and outcome, and then calculated an overall summary of the sOR across all comparisons (ssOR). We included 25 treatment comparisons with 153 RCTs and 24,592 patients. In six of 25 comparisons (24%), off-label drugs were significantly superior (five of 25) or inferior (one of 25) to approved treatments. Overall, off-label drugs were more favorable than approved treatments (ssOR 0.72; 95% CI = 0.54-0.95) but there was heterogeneity.

**Conclusions and Relevance:** Approval status does not reliably indicate which drugs are more favorable in situations with clinical trial evidence comparing off-label with approved use. Drug effectiveness assessments without considering off-label use may provide incomplete information. To ensure that patients receive the best available care, funding, policy, reimbursement, and treatment decisions should be evidence based considering the entire spectrum of available therapeutic choices.


**Background:** We evaluated the benefits and harms of adjunctive corticosteroids in adults hospitalized with community-acquired pneumonia (CAP) using individual patient data from randomized, placebo-controlled trials and to explore subgroup differences.

**Methods and results:** Data from 1506 individual patients in 6 trials were analyzed using uniform outcome definitions. Within 30 days of randomization, 37 of 748 patients (5.0%) assigned to corticosteroids and 45 of 758 patients (5.9%) assigned to placebo died (adjusted odds ratio [aOR], 0.75; 95% confidence interval [CI], .46 to 1.21; P =.24). Corticosteroids compared to placebo reduced time to clinical stability and length of hospital stay by approximately 1 day with corticosteroids but lead to hyperglycemia (160 [22.1%] vs 88 [12.0%]; aOR, 2.15; 95% CI, 1.60 to 2.90; P < .001) and CAP-related rehospitalization (33 [5.0%] vs 18 [2.7%]; aOR, 1.85; 95% CI, 1.03 to 3.32; P = .04).

**Conclusions and relevance:** Adjunct corticosteroids for patients hospitalized with CAP reduce time to clinical stability and length of hospital stay by approximately 1 day without a significant effect on overall mortality but with an increased risk for CAP-related rehospitalization and hyperglycemia.


**Background:** Single-tablet regimens for patients with HIV infection starting antiretroviral therapy are highly used but regimens taken as separate drugs might be as effective and cost less. We assessed whether the one pill once a day combination of efavirenz, emtricitabine and tenofovir reduces the risk of disease progression compared with multiple-pill formulations of the same regimen.

**Methods and Results:** We selected patients starting one-, two- or three-pill formulations of this regimen in the Antiretroviral Therapy Cohort Collaboration and followed them until an AIDS event, death or until regimen change. Among 11,739 patients starting the regimen, there were 386 AIDS events and 87 deaths and many patients switched to the same regimen with fewer pills. Two pills rather than one was associated with an increase in the risk of AIDS or death [hazard ratio (HR) 1.39; 95% confidence interval (CI) 1.01-1.91], but three pills rather than two did not appreciably add to that increase (HR 1.19; 95% CI 0.84-1.68). We estimate that 77 patients would need to be exposed to a one-pill regimen rather than a three-pill regimen for 1 year to avoid one additional AIDS event or death.

**Conclusions and Relevance:** This particular single-tablet regimen is associated with a modest decrease in the risk of AIDS or death relative to multiple-pill formulations.
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>
<thead>
<tr>
<th>Senior Researcher</th>
<th>h-Index$^1$</th>
<th>Standard value$^2$</th>
<th>Mean citation frequencies per publication</th>
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<tbody>
<tr>
<td>PD Dr. M. Briel</td>
<td>41</td>
<td>2.1</td>
<td>41.71</td>
</tr>
<tr>
<td>Prof. H.C. Bucher</td>
<td>56</td>
<td>2.3</td>
<td>42.38</td>
</tr>
<tr>
<td>PD Dr. S Dell-Kuster</td>
<td>11</td>
<td>1.2</td>
<td>8.4</td>
</tr>
<tr>
<td>PD Dr. L. Hemkens</td>
<td>11</td>
<td>1.2</td>
<td>22.24</td>
</tr>
<tr>
<td>PD Dr. B. Kasenda</td>
<td>12</td>
<td>1.3</td>
<td>7.72</td>
</tr>
<tr>
<td>PD Dr. M. Koller</td>
<td>31</td>
<td>2.2</td>
<td>15.02</td>
</tr>
<tr>
<td>Prof. A. Nordmann</td>
<td>26</td>
<td>1.6</td>
<td>26.99</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.

2) 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.

Figure 1.
Citation frequency and number of indexed publications of senior researchers of CEB from 2001 to 2017 (Thompson Science Citation Index)
CEB RESEARCH

In 2017 researchers of CEB have published 78 publications in peer reviewed journals.

Methodological research
Methodological research constitutes a major part of our research activity and in 2017 we published 19 methodological papers (1-4,8,18,21,22,26,28,53,55,62,63,69,71-74). Four publications dealt with health equity in GRADE guideline development (2,21,72,74). Five papers dealt with various methodological aspects of trial discontinuation (3,4,8,53,72). Four publications illustrated important issues related to reporting and reporting bias of clinical research results (1,22,55,63). Two publications dealt with costs of randomized controlled trials (62,63), and two reports dealt with the development of guidance for judging the quality of clinical research (69,70). Further publications examined the consistency and quality of research results reported in observational and randomised controlled trials investigating the same research question and treatment effects of off-label drug use (18,21,26,28).

Evidence synthesis
Evidence synthesis is one of our strengths. We have published four meta-analyses, investigating low intensity ultrasound for bone healing (52), knee arthroscopy versus conservative management for degenerative knee problems (9), procalcitonin to discontinue antibiotics in acute respiratory tract infections (58), effectiveness of return to work programs (Cochrane review 68) and surgery for sleep apnea (Cochrane protocol 75). We conducted and participated in two individual patient data meta-analyses on corticosteroids in community acquired pneumonia (7), and procalcitonin-guide antibiotic therapy and mortality (57) and in one network meta-analysis on secondary antiretroviral therapy (25).

Randomised controlled trials
We finished one trial in anaesthesiology (14) and started a large nationwide trial of routine prescription feedback and monitoring to reduce antibiotic use in primary care (NFP 72 Anti-microbial Resistance).

Real world evidence
Eight publications come from our international collaboration in observational data analyses in HIV covering important topics such as the effect of delayed antiretroviral treatment initiation in elderly patients (12, 30, 31, 34, 47, 64, 76, 78) and seven publications from collaborations with the Swiss HIV Cohort Study (5, 6,20,38,50,60,66). Two publications from collaborations with the Harvard School of Public Health and Stanford University dealt with individualized HIV viral monitoring strategies in different care settings (12, 38). Sabin Nszanimana PhD student from Rwanda contributed five publications (15,25,39,40,65). In two papers, both published in Lancet HIV he investigated the effectiveness of second line antiretroviral therapy in resources limited settings (25) and the incidence of HIV in Rwanda (39). Two publications based on data from Europe and Canada dealt with acute hepatitis C reinfection and treatment in advanced liver disease (77,78).

1 Number refers to the list of publication (see section "Publications of CEB in 2017").
Team of Biostatisticians
PD Dr. Salome Dell-Kuster, Dr. Soheila Aghlmandi, Dr. Giusi Moffa (Dr. Jim Young absent)

Clinical Epidemiology & Methodology Team
PD Dr. Matthias Briel, Dr. Viktoria L. Gloy, Aviv Ladanie, Hannah Ewald, Benjamin J. Speich, PD Dr. Lars G. Hemkens (Kimberly McCord, Dmitry Gryaznov, PD Benjamin Kasenda 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 2017 were 167 hours, this is an increase of 24% compared to the previous year. In 2017, CEB was training 7 PhD students and 6 Master students. PhD and master students have been involved in eight publications (4,15,22,25,28,39,40,65) and were first or senior authors in six publications (14,15, 28,36,39,40).

CEB CONSULTING

CEB is providing clinical epidemiology consultancy services within the Department Clinical Research at the University Hospital Basel. Seven publications originated from collaborative projects with the Department of Surgery (23,24,33,37,48,54,70). Consultancy for industry resulted in one publication on real world data for the treatment of chronic hepatitis C in patients with advanced liver disease (77).

HEALTH TECHNOLOGY ASSESSMENT (HTA)

CEB has completed one HTA report on combination therapy compared to monotherapy for moderate to severe Alzheimer’s Disease that was commissioned by the Swiss Medical Board. The report showed that combination therapy lead to small improvement in cognitive functions compared to monotherapy.

The institute holds one additional consultancy mandate for Health Technology Assessment from the Swiss Federal Office of Public Health and this report is going to be finished in 2018.

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. This network was officially approved by the rectorat of the University of Basel in spring 2017.
The Swiss Transplant Cohort Study (STCS) was founded in 2007 with major support of CEB. 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 2017 4574 solid organ transplanted patients have been included into the study. In total 14 studies have been published in 2017, with 2 studies (13, 29,) where collaborators of the data center are co-authors (for details see www.stcs.ch).

Health Technology Assessment Team
Prof. Heiner C. Bucher, Dr. Soheila Aghlmandi,
Dr. Viktoria L. Gloy, Dr. Dominik Glinz
CEB has expanded its scientific network and collaboration with clinical researchers in 2017. This has led to a marked increase in publications. It will be important to obtain core funding to realize more own research projects in the coming years.

It is a great pleasure to work with such a motivated team of young researchers and my thanks go to the entire team. I want to particularly thank Diana Grauwiler, the clinical research manager of the institute for project management, budgeting and financial control, and administration of CEB.

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


(8) Briel M, Elger BS, von Elm E, Satalkar P. Insufficient recruitment and premature discontinuation of clinical trials in Switzerland: Qualitative study with trialists and other stakeholders. *Swiss Med Weekly* 2017;147:w14556


(28) Ladanie A, Ioannidis JPA, Stafford RS, Ewald H, Bucher HC, Hemkens LG. Off-label treatments were not consistently better or worse than approved drug treatments in randomized trials. *J Clin Epidemiol* 2017 Nov 13. Epub [ahead of print].


Research Letters, Letters and Non-Peer Reviewed Publications


Reports


Presentations


**Posters and Abstracts**


Venia docendi University of Basel (Assistent professorships)

PD Dr. Salome Dell-Kuster Perioperative patient safety – The perspective of the patient, the clinician and the clinical researcher University of Basel Oct 5, 2017.

PD Dr. Benjamin Kasenda Planning, conduct, and reporting of randomized trials – wading the mist of clinical research, University of Basel Oct 4, 2017.


Awards

Hannah Ewald received the Thomas C Chalmers award at the Global Evidence Summit in Cape Town, South Africa, 2017, September 14 for her poster ‘Agreement of treatment effects from non-randomized studies using causal modelling and randomized trials: a meta-epidemiological study’ for the best oral and poster presentation addressing methodological issues related to systematic reviews given by an early career investigator.

Lars Hemkens received the David Sackett Award by Deutsche Netzwerk Evidenz basierte Medizin at the 18th Annual Meeting in Hamburg, Germany 2017, March 10 for his publication ‘Agreement of treatment effects for mortality form routinely collected data and subsequent randomized trials: Meta-epidemiological survey’ published in BMJ 2016; 352:i493.
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 serves as a member of the steering committee of CASADE and the institute is collaborating in various projects. For details see individual projects or www.CASCADE-Collaboration.org
Start of project: 01.01.2010 – End of project: 31.01.2017

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: 31.10.2017

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. 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.

Routinely collected data for randomized trials: promises, barriers, and implications*
A project aiming to collect barriers and limitations related to implementing routinely collected data (RCD) in randomized clinical trials (RCTs) and discussing the three main potential benefits of RCD in trials: increasing value through better feasibility, through expanding the research agenda, and through improving design and data collection options.

Tutorial assistance for board certification in surgery: Frequency, associated time and costs*
Tutorial assistance is related to extra time and cost. We aimed at quantifying the extra time and resulting cost in the operating theatre to train one surgical resident for board-certification in Switzerland. Of the 212'948 operations carried out between 2008-2012, residents performed about 1/3 of all operations, rendering it difficult to get board-certification within a reasonable period of time. An increase in duration and cost of well-defined procedures categories e.g. cholecystectomies was demonstrated if a resident performed the procedure. In less well-defined categories, residents seemed to perform less difficult procedures than senior consultants resulting in shorter duration of the surgery. The financial impact of tutorial assistance is important and solutions need to be found to compensate for this activity.
Start of project: 26.01.2012 – End of project: 30.06.2017

2 *Project Leadership ± Project Partner
Efficacy and safety of low-dose corticosteroids in patients with community acquired pneumonia: Systematic review and individual patient-data meta-analysis of randomized trials

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: 30.06.2017

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: 31.12.2017

ONCOLOGY

Presence of bone marrow micro-metastases in stage I-III colon cancer patients is associated with worse disease-free and overall survival

The relevance of bone marrow micro-metastases (BMM) as a prognostic factor for disease free (DFS) and overall survival (OS) was investigated in a prospective multicenter cohort study including 144 stage I-III colon cancer patients undergoing bone marrow aspiration from both iliac crests prior to open oncologic resection. DFS and OS were analyzed using a Cox proportional hazard model and robust standard errors to account for clustering in the multicenter setting. Median overall follow-up was 6.2 years with no losses to follow-up. BMM occur in over one third of stage I-III colon cancer patients and are a significant, independent negative prognostic factor for DFS and OS. Future trials should evaluate whether node-negative colon cancer patients with BMM benefit from adjuvant chemotherapy.

Start of project: 23.12.2013 – 31.05.2017

HTA REPORTS

HTA report - Combination therapy compared to monotherapy for moderate to severe Alzheimer's Disease

Alzheimer’s disease is a serious neurocognitive disorder which is characterized by a progressive decline of cognitive functions and memory. Cholinesterase inhibitors are given for mild to moderate dementia, while memantine is given for moderate to severe dementia. Both substances can be co-administered in dementia of intermediate severity but in contrast to the practice in most other European countries the Swiss mandatory basic health insurance only covers either a cholinesterase inhibitor or memantine but not the combination therapy. The aim of this HTA report was to assess the effectiveness and safety, the cost-effectiveness and budget impact, legal as well as ethical implications of the combination therapy with memantine and a cholinesterase inhibitor compared to monotherapy with a cholinesterase inhibitor or memantine in patients with moderate to severe Alzheimer’s Disease and Mini-Mental State Examination score (MMSE) of 19 or less.

Start of project: 12.02.2015 – End of project: 31.08.2017
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: 30.5.2018

SHCS 805 Drug-in Drug Interactions*
Potential drug-drug interactions (DDI) are the most common drug-related problem in ambulatory care and a growing problem in HIV infection due to increasing comorbidities and age of HIV-infected patients. In this study of the Swiss HIV Cohort Study (SHCS) we assess the prevalence of contraindicated and potential clinically relevant DDIs and determine major patients and provider related predictors of DDIs in patients receiving antiretroviral therapy. Finally we validate drug data entered into the new Webmed database of the SHCS with a probability matched patient sample of claim data of Helsana, the largest Swiss health insurer.
Start of project: 01.02.2018 – End of project: 31.12.2018

SHCS 832 Estimating the effectiveness of NRTI sparing regimens in patients with limited treatment options and then re-estimating as data accrue*
Novel NRTI sparing regimens with dolutegravir are already in use within the SHCS. There is no good evidence that these regimens are better than earlier regimens used to treat NRTI intolerant patients. We will develop a framework based on Bayesian methods for routinely updating estimates of effectiveness as data accrue. This would provide the best information currently available about novel regimens for clinicians treating patients with limited treatment options. We will: (1) Develop a appropriate measure of regimen durability given the information available from the SHCS ; (2) Describe a Bayesian statistical method for estimating the relative effectiveness of novel regimens given limited time to event data and for then updating those estimates; (3) Provide up-to-date estimates of the relative durability of novel regimens used to treat NRTI intolerant patients.
Start of project: 01.10.2017 – End of project: 31.01.2019

SHCS 819 HIV and co-morbidity related costs in Switzerland: A large scale data linkage study*
Studies based on respresenative data on costs and resource use of chronic conditions in Switzerland are scare. Likewise in HIV there is a lack of high quality cost data. With the success of antiretroviral therapy (ART) HIV infection has become a chronic condition but comorbidities due to cardiovascular diseases, cancer and liver cirrhosis are becoming increasingly important. Therefore, HIV infection is an important and prominent disease to study the cost and consequences of comorbidity in a condition requiring lifelong care and drug treatment. We propose to investigate health resource use and consequences for management of HIV and non-HIV related comorbidities by matching claim data from health insurers with data from the Swiss HIV Cohort Study by anonymous privacy preserving linkage.
Start of project: 01.05. 2018 – End of project: 30.09.2019
Smartphone app and CO selfmonitoring 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 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: 31.12.2018

METHODOLOGICAL RESEARCH PROJECTS

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: 31.03.2018

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: 30.11.2018

Epidemiology and publication of discontinued randomised trials; DISCO

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.

Start of project: 03.02.2014 – End of project: 31.03.2018

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.

Effects of the Swiss human research legislation on the costs of RCTs*

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: 31.03.2018

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: 31.03.2018

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.

Start of project: 01.04.2013 – End of project: 30.10.2018

„Beschreibende Statistik der Forschung im Geltungsbereich des Schweizer Humanforschungsgesetzes (HFG)” (subproject 1) und „Befragung der Forschenden zur Umsetzung des HFG” (subproject 2)*

Starting January 2016 all applications to research ethics committees (RECs) in Switzerland need to be submitted and managed through a central online portal (BASEC). This project comprises 3 parts: 1) A descriptive analysis of the BASEC content (all studies sent to Swiss RECs) for 2016/2017 and then yearly updates until 2021; 2) a survey of researchers/principal investigators of studies submitted via BASEC in 2017; and 3) to describe research projects for which applicants were uncertain whether they are within the scope of the Human Research Act or not. The project is done in collaboration with the Swiss Clinical Trial Organisation and Cochrane Switzerland.

Start of project: 15.12.2017 – End of project: 30.09.2018

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: 30.09.2018
NFP72: Routine Antibiotic Prescription*
Antibiotic resistance is a worldwide problem and associated with the direct use of antibiotics in the population. Most antibiotics are used in primary care for acute respiratory tract infections, although primarily of viral origin, and urinary tract infections (UTI). In a nationwide pragmatic randomized intervention trial we use routinely collected fully anonymized claim data from 4 large health insurers covering 40% of insurees in Switzerland and investigate whether routine antibiotic prescription feedback in primary care physicians reduce antibiotic use. We will link claim data with national antibiotic resistance data by anonymized probabilistic record linkage to investigate whether the intervention affects resistance of bacteria against broad spectrum antibiotics for URTI.
A health economic evaluation will be integrated part of the trial.
Start of project: 01.01.2017 – End of project: 30.05.2020

CEIT – Cancer (Comparative Effectiveness of Innovative Treatments for Cancer)*
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. The ultimate goal is to provide decision-makers with guidance to identify early indications 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: 01.01.2019

Concordance of treatment effects of 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.
Start of project: 20.03.2013 – End of project: 31.12.2018

Impact of non-standardized outcome analyses on clinical care of HIV patients: meta-epidemiological study*
We conduct a meta-epidemiological study evaluating a large number of recently published trials on antiretroviral treatment in HIV. Results are recalculated using various alternative approaches to deal with missing data. Implications on clinical interpretation of the trial results are assessed. We aim to provide healthcare decision makers with an empirical estimate of the impact of non-standardized outcome 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: 31.01.2019

Routinely collected health data for randomized trials – The RCD for RCT initiative*
Large and simple pragmatic mega-trials may be conducted with only a fraction of costs when using routinely collected health data (RCD). The RCD for RCT initiative aims on improving how clinical trials are made, driven by a strong belive that most of the problems of randomized clinical trial (RCT) evidence are man-made and routine data can be a key to solve many of these issues.
Start of project: 01.02.2016 – End of project: 31.12.2030

The application of Electronic Health Records in clinical trial research: A systematic review*
Electronic Health Records (EHRs) may facilitate randomized clinical trials (RCTs), mainly by using pre-existing data infrastructures for recruitment and outcome assessment and potentially saving
costs, time, and other resources. We perform a systematic review of the literature assessing the current use and value of EHR in clinical trials.

Start of project: 15.01.2016 – End of project: 31.6.2018

Development of a reporting guideline for RCTs using routinely collected data (RCD)*
This project assesses the reporting gaps in RCD trials, followed by a stakeholder qualitative process for the development of a reporting guideline and checklist. The qualitative process will encompass a survey to stakeholders such as clinical researchers, clinicians, publishers and pharmaceutical industry representatives; and we will closely collaborate with the RECORD and CONSORT groups.
Start of project: 01.03.2018 – End of project: 31.12.2019

The agreement of treatment effects from randomized trials using routinely collected data (RCD) or actively collected data: Meta-epidemiologic analysis*
To determine whether using RCD sources (such as a disease registry or EHR) to measure outcomes of clinical trials leads to different estimates due to a variability in their data validity, we perform a meta-epidemiological analysis comparing the treatment effects measured by different RCD sources against an active data source (traditional RCT).
Start of project: 15.01.2016 – End of project: 31.12.2018

Prediction of recruitment in randomized clinical trial*
The objectives of this study are 1) to establish a comprehensive sample of randomized clinical trials with individual patient recruitment data; and 2) to develop tools to monitor and predict recruitment. The overall goal of this project is to provide clinical research, trial lists, ethics committees and funding bodies with guidance how to effectively improve patient recruitment in clinical studies.
Start of project: 01.01.2017 – End of project: 01.05.2018

The agreement of treatment effect estimates from rapid reviews using abbreviated literature searches and traditional Cochrane reviews: a meta-epidemiological study*
The agreement of effect estimates obtained from abbreviated literature searches (as conducted in rapid reviews) and those obtained from extensive searches (as performed in Cochrane or Campbell reviews) is unknown. The objective of this study is to assess differences between treatment effects estimated from abbreviated and extensive literature searches. Our results will systematically quantify the impact of faster and abbreviated searching on treatment effect estimates across a wide range of Cochrane Systematic Review topics.
Start of project: 01.07.2016 – End of project: 31.12.2018

ANESTHESIOLOGY

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 (none prospectively validated) for reporting intraoperative complications. Our group developed a definition and classification for intraoperative complications within a Delphi study involving international interdisciplinary experts. As both surgery and anaesthesia may be involved in complications, all patient-related intraoperative complications 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
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 results of the RCTs on PIEB in regards of motor function seem to be generalizable to women not eligible in these trials, but these women (non-trial patients) required a higher time-weighted number and volume of additional rescue top-ups. This higher number and volume of rescue top-ups in non-trial patients suggests that their labor is more intense, which should be considered in the dosing scheme for PIEB labor analgesia in non-trial patients.

Start of project: 11.02.2015 – End of project: 31.06.2018

Systematic review and simulation study of ignoring clustered data in surgical trials*

Multiple surgical procedures in a single patient are relatively common and lead to dependent (clustered) data. This dependency needs to be accounted for in study design and data analysis. A systematic review between 2004 and 2013 was performed to assess how clustered data were handled in RCTs including patients undergoing unilateral or bilateral inguinal hernia repair. Study characteristics determining the appropriateness of handling clustered data were extracted. Using simulations, various statistical methods accounting for clustered data were compared with an analysis ignoring clustering.

Clustering was rarely considered in inguinal hernia trials. The simulations underline the importance of considering clustering as part of the statistical analysis to avoid false-positive and false-negative results, and hence inappropriate study conclusions.

Start of project: 01.02.2013 – End of project: 31.01.2018

HTA REPORTS

HTA report – Iron therapy for iron deficiency without anaemia*

Several symptomatic populations have been suggested to benefit from iron therapy if they have iron deficiency no anaemia (IDNA). So far though the effectiveness of the therapy with iron is unclear for symptomatic IDNA and there is even no consensus regarding the relevant diagnostic markers and thresholds that should be used to diagnose IDNA. The aims of this reports are: 1) to assess the effectiveness of iron therapy in populations with symptomatic IDNA with a systematic review, 2) to assess diagnostic markers with an individual patient data meta-analysis in population with relevant treatment effect which were identified within the systematic review and 3) to assess costs of intravenous versus oral treatment in the populations identified in the systematic review.

Start of project: 01.02.2017 – End of project: 30.06.2018

HTA report – Assessment of knee arthroscopy for the treatment of degenerative changes*

The rate of knee arthroscopies has increased by 20% between 2005 and 2011. The aims of this report are 1) to assess the clinical effectiveness and safety of therapeutic knee arthroscopy compared to any other treatment in patients with degenerative changes of the knee – irrespective of whether they are primarily due to meniscal damage, osteoarthritis of the knee or a mix of both, 2) to assess the clinical effectiveness and safety of therapeutic knee arthroscopy in inpatient compared to outpatient, 3) to assesses the cost-effectiveness and budget impact of therapeutic knee arthroscopy compared to any other treatment in patients with degenerative changes of the knee primarily due to meniscal damage and 4) inpatient compared to outpatient therapeutic knee arthroscopy in patients degenerative meniscal changes.

Start of project: 01.01.2017 – End of project: 13.04.2018
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 2017 were 167 hours. H.C. Bucher and M. Briel coordinate three teaching blocks in undergraduate medical training (Wissenschaftliche Kompetenz, Patienten Orientierte und Evidenz-basierte Medizin (POEM), and Wissenschaftsmonat).

Postgraduate

7. M. Briel. Scientific set-up, systematic reviews and meta-analysis. Research question development and study design. Sponsor-Investigator course in Good Clinical Practice, University Hospital Basel, spring semester.
8. M. Briel. Scientific set-up, systematic reviews and meta-analysis. Research question development and study design. Sponsor-Investigator course in Good Clinical Practice, University Hospital Basel, fall semester.

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. Julian Bühler. Faculty of Medicine, University of Basel. Comparative effectiveness of tenofovir in HIV-infected treatment-experienced and naive patients: systematic review supervised by L.G. Hemkens.
3. Roy Frei. Faculty of Medicine, University of Basel. Empirical research on discontinuation and registration of randomized clinical trials supervised by M. Briel.
4. 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. Katherine Winkel. Faculty of Science, Epidemiology, University of Basel. Impact of non-standardized outcome analyses on clinical care of HIV patients: A meta-epidemiological study supervised by L.G. Hemkens.
6. Kimberly McCord. Faculty of Science, Epidemiology, University of Basel. Pragmatic randomized trials using routinely collected health data: A meta-epidemiological study supervised by L.G. Hemkens.
Supervision of MD Theses

1. **Alain Amstutz**. Discontinuation and non-publication of randomized clinical trials supported by the main public funding body in Switzerland: a retrospective cohort study supervised by M. Briel.

PhD Students (Epidemiology)

2. **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.
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<thead>
<tr>
<th>Name</th>
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<tr>
<td>Prof. Dr. med. Heiner C. Bucher, MPH</td>
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<td>Kübra Özoglu, MSc</td>
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