Routine antibiotic prescription and resistance feedback in primary care: A nationwide pragmatic randomized controlled trial

Clinical Study Protocol

Study Type:	Pragmatic randomized controlled trial
Study Categorisation:	Category A pragmatic trial
Study Registration:	Planned: clinicaltrials.gov and kofam.ch
Study Identifier:	CEB-NFP72
Sponsor-Investigator:	Prof. Heiner C. Bucher, MD MPH Basel Institute for Clinical Epidemiology and Biostatistics (ceb) University Hospital Basel, Spitalstrasse 12 CH-4031 Basel, Switzerland Phone +41 61 556 5100; Fax +41 61 265 3109 Email: heiner.bucher@usb.ch
Investigators:	PD Dr. Andreas Kronenberg, MD Institute for Infectious Diseases University of Bern, Bern, Switzerland Dr. Julia Bielicki, MD MPH Infectious Diseases and Paediatric Pharmacology University Children's Hospital Basel, Basel, Switzerland and St. George's University London, London, UK Prof. Andreas Zeller, MD MSc Centre for Primary Health Care, University of Basel, Basel, Switzerland Prof. Andreas Widmer, MD. MS Division of Infectious Diseases and Hospital Hygiene, University Hospital Basel, Basel, Switzerland
Investigational Product:	Not applicable / Pragmatic trial in usual care
Protocol Version and Date:	Version 1.1, July 12th 2017

CONFIDENTIAL

The information contained in this document is explicitly not confidential.

Signature Pages

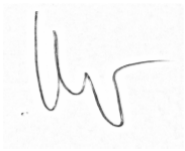
Study number	CEB-NFP72
Study Title	Routine antibiotic prescription and resistance feedback in primary care: A nationwide pragmatic randomized controlled trial

The Sponsor-Investigator and trial statistician have approved the protocol version [1 (dated 18.05.2017)], and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor-Investigator:

Prof. Heiner C. Bucher, MD MPH

Basel, 12.07.2017



Principal Investigators:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Principal investigators	PD Dr. Andreas Kronenberg, MD, Institute for Infectious Diseases, University of Bern, Bern, Switzerland
	Dr. Julia Bielicki, MD MPH, Infectious Diseases and Paediatric Pharmacology University Children's Hospital Basel, Basel, Switzerland and St. George's University London, London, UK
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PD Andreas Kronenberg

Bern, 12.07.2017

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London, 12.07.2017

Prof. Andreas Zeller

Basel, 12.07.2017

Prof. Andreas Widmer

Basel, 12.07.2017

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158 **STUDY SYNOPSIS**

Sponsor / Sponsor-Investigator	Prof. Heiner C. Bucher, MD MPH Basel Institute for Clinical Epidemiology and Biostatistics University Hospital Basel Spitalstrasse 12 CH-4031 Basel, Switzerland Phone +41 61 556 5100; Fax +41 61 265 3109 Email: heiner.bucher@usb.ch
Study Title:	Routine antibiotic prescription and resistance monitoring in primary care physicians: A nationwide pragmatic randomized controlled trial
Short Title / Study ID:	CEB-NFP72
Protocol Version and Date:	Version 1.1 July 11th 2017
Trial registration:	Planned: clinicaltrials.gov and kofam.ch
Study category and Rationale	Category A (no pharmaceutical product, medical device or transplant are involved in this trial)
Clinical Phase:	Phase 4
Background and Rationale:	Antibiotic resistance is an increasingly serious problem in Switzerland which is associated with the exposure and overall uptake of antibiotics in a population. Reduced antibiotic prescribing for outpatients is paralleled by a decrease in antibiotic resistance rates. In a recent pragmatic trial we found only promising yet not very conclusive results as those were present only in some groups. This nationwide antibiotic stewardship program with routine feedback on antibiotic prescribing was not associated with an overall change of antibiotic use. In older children, adolescents, and younger adults less antibiotics were prescribed, but not consistently over the entire intervention period. Hence, we now we aim to evaluate a better tailored program to obtain a better understanding of the effects on patient-relevant outcomes, on antibiotic resistance, and of the underlying mechanisms leading to different effects in certain subgroups of patients. We plan to evaluate a nationwide antibiotic stewardship program combining routine prescription and resistance feedback with the provision of physician and patient education material within a large-scale pragmatic randomized controlled trial in primary care physician in Switzerland. The project would be conducted within the framework of the National Program NFP 72 on antimicrobial resistance by the Swiss National Science foundation

Objective(s):	To evaluate whether this nationwide antibiotic stewardship program reduces the total amount of antibiotics used in primary care.
Outcome(s):	Primary outcome: overall antibiotic use, defined as prescribed defined daily doses (DDD) of antibiotics per 100 patient consultations (total patient population) evaluated over a period of 12 months, from month 13 to month 24 post randomization (longer term intervention effect). Secondary outcomes: (1) Overall antibiotic use defined as prescribed DDD of antibiotics per 100 patient consultations evaluated over a period of 12 months, from month 1 to 12 post randomization (short-term intervention effect); (2) Overall antibiotic use defined as prescribed DDD of antibiotics per 100 patient consultations evaluated over a period of 24 months, from month 1 to month 24 post randomization, with two repeated measurements, over the first and the second 12 month period post randomization; (3) Use of broad spectrum antibiotics in the total patient population (DDD of this specific type per 100 consultations) a. quinolones b. oral cephalosporines ; (4) Hospitalizations rates a. all-cause b. related to infections (DRG-based definition) (5) Antibiotic use (DDD per 100 consultations) in four specific age groups, in patients a. <6 years b. 6 to <18 years c. 18 to <65 years d. ≥ 65 years (6) Secondary outcomes (3) to (5) will be evaluated over two 12 month periods (from month 1 to month 12, and from month 13 to month 24).
Study design:	Pragmatic, randomized controlled trial entirely based on routinely collected data
Inclusion / Exclusion criteria:	<u>Inclusion Criteria:</u> ▪ Primary care physicians in Switzerland board certified with FMH title in general internal medicine or paediatrics & adolescent medicine ▪ Above the 25th percentile of antibiotic prescribing ▪ consulting with at least 100 patients per year ▪ with individual Zahlstellenregister number. There are no exclusion criteria.

Measurements and procedures:	All measurements are based on anonymized routinely collected insurance data provided quarterly by health insurers. No data are collected for the purpose of this study or by any direct patient contact or interaction with physicians.
Intervention:	The intervention is a combined antibiotic stewardship program. Physicians receive eight times (quarterly over 24 months, first in October 2017) by postal mail a feedback on their antibiotic prescriptions and updated antibiotic resistance information from the community and served patient population. The feedback is based on anonymized insurance data and includes only aggregated patient-related information (for example prescription rates in age-groups). With the first letter, educational material targeting physicians (evidence-based guidelines for conditions leading to most outpatient prescriptions in primary care) and patients (validated information material on using antibiotics wisely) are provided. Individual antibiotic prescription data will also be made available on a study website that can be accessed by each physician in the intervention group by an unique access code.
Control:	Usual care without any material or feedback.
Number of Participants with Rationale:	We aim to detect a minimum reduction of total antibiotic prescriptions by 5% in the intention to treat population with a statistical power of 90%. This corresponds 2590 physicians randomized (we will randomize 2590 physicians in a 2:1 ratio to the intervention (n=1725) and control group (n=865)). We deem this 5% reduction of antibiotic prescriptions a minimally public health relevant effect on a nationwide level in Switzerland.
Study Duration:	24 months
Study Schedule:	October 2017 to September 2019
Investigator(s):	Prof. Heiner C. Bucher, MD MPH, Basel Institute for Clinical Epidemiology and Biostatistics University Hospital Basel PD Dr. Andreas Kronenberg, MD, Institute for Infectious Diseases, University of Bern, Bern, Switzerland Julia Bielicki, MD, MPH, Infectious Diseases and Paediatric Pharmacology University Children's Hospital Basel, Basel, Switzerland and St. George's University London, London, UK Prof. Andreas Zeller, MD, MSc, Centre for Primary Health Care, University of Basel, Basel, Switzerland Prof. Andreas Widmer, MD,MS Division of Infectious Diseases and Hospital Hygiene, University Hospital Basel, Basel, Switzerland PD Matthias Schwenkglenks, PhD, Institute of Pharmaceutical Medicine, University of Basel, Basel, Switzerland

Study Centre(s):	Single-center: Basel Institute for Epidemiology and Biostatistics (CEB), University Hospital Basel, Department of Clinical Research
Statistical Considerations:	The intervention effect on the primary endpoint will be evaluated by comparing the intervention and the control group by means of ANCOVA modelling including baseline as a covariate. The sample size was derived to ensure a statistical power of 90% to compare the intervention group to control at 0.05 significance level, and assuming a minimum meaningful reduction in total antibiotics prescription by 5%. Secondary outcomes, including the response over the first year post-randomization, endpoints specific to broad spectrum antibiotics and response stratified by age groups, will be also explored by means of ANCOVA modelling. Hospitalization rates in the intervention and control group will be modelled by means of logistic regression.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

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STUDY SUMMARY IN LOCAL AND PLAIN LANGUAGE

Routine Feedback zu Antibiotikaverordnungen und Resistenzentwicklung in der Grundversorgung

Hintergrund: Antibiotikaresistenzen stehen in direktem Zusammenhang mit der Verschreibungshäufigkeit. In den letzten fünf Jahren hat sich die Anzahl resistenter Keime mehr als verdoppelt. Erfahrungswerte zeigen, dass eine zurückhaltende Verschreibungspraxis von Antibiotika zu einer Verminderung von Resistenzen führt. Am meisten Antibiotika werden in der Grundversorgung verschrieben.

Ziele: In einer nationalen Interventionsstudie soll untersucht werden, ob Antibiotikaverschreibungen reduziert werden können, wenn Ärzte evidenzbasiertes Informationsmaterial und Rückmeldungen zu ihren verordneten Antibiotika und der Resistenzlage erhalten.

Methoden: Mit Abrechnungsdaten der drei grössten Krankenversicherer CSS, Helsana und Sanitas mit 3.8 Mio Versicherten (40% der Schweizer Bevölkerung) sollen die Antibiotikaverschreibung von Hausärzten ausgewertet werden. 2590 Ärzte erhalten entweder Behandlungsleitlinien zu Atemwegs- und Harnwegsinfekten und Patienteninformationsmaterial sowie über 2 Jahre regelmässig Rückmeldung zu ihren Antibiotikaverschreibungen und zur Resistenzentwicklung in ihrem Versorgungsgebiet, oder sie erhalten keine Informationen. Für diese Studie erhalten die Studienleiter ausschliesslich anonymisierte Daten und können Ärzte und Patienten nicht identifizieren.

Wir streben eine 5% Reduktion der Antibiotikaverschreibung durch an der Studie teilnehmende Ärzte an. Wir untersuchen die Verschreibung von Antibiotika nach Altersgruppen, Gebrauch von Breitspektrumantibiotika, sowie die Häufigkeit von Krankenhauseinweisungen aufgrund von Infekten.

Bedeutung / möglicher Nutzen: Die Resultate sollen Auskunft zur Wirksamkeit eines routinemässigen Feedbacks bei Antibiotikaverschreibungen geben. Die Studie wird breit unterstützt, u.a. im Rahmen des Nationalen Forschungsprogramms (NFP) 72 durch den Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung (SNF), durch die FMH (Verbindung der Schweizer Ärztinnen und Ärzte) und von den drei grössten Krankenversicherern CSS, Helsana und Sanitas. Die epidemiologischen Ergebnisse der Studie sind von grossem Nutzen für zukünftige grundlegende Entscheidungen und Strategieentwicklungen in der schweizerischen Gesundheitspolitik.

ABBREVIATIONS

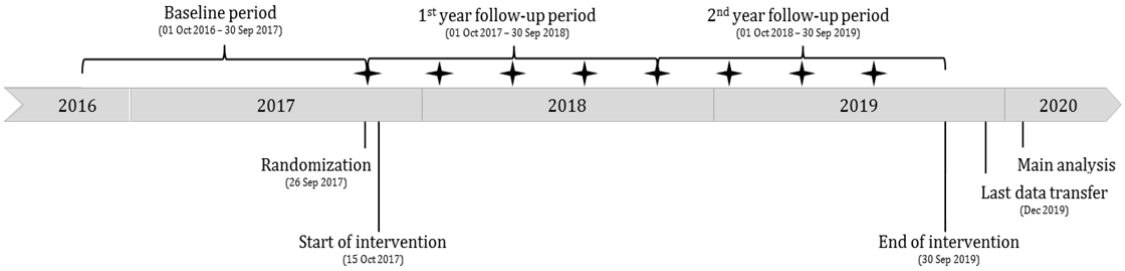
AE	Adverse Event
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CRF	Case Report Form
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin)*
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
IB	Investigator's Brochure
Ho	Null hypothesis
H1	Alternative hypothesis
HFG	Humanforschungsgesetz (Law on human research)
IMP	Investigational Medicinal Product
ISO	International Organisation for Standardisation
ITT	Intention to treat
KlinV	Verordnung über klinische Versuche in der Humanforschung *(in English: ClinO, in French OClin)*
MD	Medical Device
OClin	Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain *(in German : KlinV, in English : ClinO)*
PI	Principal Investigator
SOP	Standard Operating Procedure
SPC	Summary of product characteristics

STUDY SCHEDULE

Study Timetable

Task & Month (planned start 09/2017)	1	2	5	8	11	14	17	20	23	29
Selection and randomization (September 2017)	**x**									
Provision of feedback by postal mail		x	x	x	x	x	x	x	x	
Provision of online service		x	x	x	x	x	x	x	x	
Transfer and provision of routine data by health insurers	x	x	x	x	x	x	x	x	x	x
Start of main data analysis										x

Timeline



1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Sponsor-Investigator

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Prof. Andreas Widmer, MD, Division of Infectious Diseases and Hospital Hygiene, University Hospital Basel, Basel, Switzerland

1.3 Statistician ("Biostatistician")

Giusi Moffa, PhD, (giusi.moffa@usb.ch, +41 61 328 51 39) Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Basel, Switzerland

1.4 Clinical Epidemiologist

Dr. med. Lars G. Hemkens, MPH (lars.hemkens@usb.ch) Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Basel, Switzerland

1.5 Laboratory

Not applicable.

1.6 Monitoring institution

See Section 1.7.

1.7 Data Safety Monitoring Committee

No data used in this study is collected for the purpose of research; therefore there is no specific data or safety monitoring committee. All data is collected for health insurers during routine care in usual practice.

However, we appoint an independent general practitioner who will serve as a guardian in case of patient or physician complaints or any potential concerns about

this study, related to perceived safety issues or otherwise, and who coordinates further action.

Ethics committees have guaranteed access to all original and processed data and permission to audit the project at any time (access to non-anonymized data must be authorized by the responsible data managers of the participating health insurers due to Swiss data protection legislation).

1.8 Any other relevant Committee, Person, Organization, Institution

Partner	Reference	Contribution
Sanitas (Zurich)	Health insurance (Cura futura group)	Provision of claims and cost data Coordination of data management processes
CSS (Lucerne)	Health insurance (Cura futura group)	Provision of claims data and contribution to health economic analysis
Helsana (Zurich)	Health insurance (Cura futura group)	Provision of claims data
Cura futura (Berne)	Association of four main health insurers	Coordination, communication, support
Swiss Medical Association (FMH, Berne)	Official association of Swiss physicians	Official supporter of the intervention program to increase impact
NFP 72 Antimicrobial Resistance	Swiss National Science Foundation	Funder and official supporter of the intervention program
Institute of Infectious Diseases (University of Berne)	Swiss Centre for Antibiotic Resistance	Provision of antibiotic resistance data Support of the intervention Expertise in antibiotic stewardship programs
Swissnoso	Developer of guidelines for prevention of nosocomial infections and antibiotic resistance	Expertise in antibiotic stewardship programs, guideline development, official supporter of the intervention program to increase impact

2. ETHICAL AND REGULATORY ASPECTS

Before the study will be conducted, the protocol (including an example of the interventional material, see Appendix 1) will be submitted to a properly constituted Competent Ethics Committee (CEC).The decision of the CEC concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study.

The study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

The trial will be registered with the trial registry of the University Hospital Basel and the U.S. National Institutes of Health (www.clinicaltrials.gov).

2.2 Categorization of study

Category A. This is a pragmatic study based entirely on routinely collected health

care data that is not specifically generated for the purpose of a study. The intervention does not pose any harm to a patient as no contact with them will be necessary, only educational information that is in agreement with best current evidence of patient information and that has been reviewed by several national and international experts in the field will be provided. The patient and physician data will be anonymized.

2.3 Competent Ethics Committee (CEC)

The Sponsor-Investigator will ensure that approval from an appropriately constituted Competent Ethics Committee (CEC) is sought for the study.

No changes of the protocol will be implemented, unless to prevent immediate danger, without prior Sponsor and Ethics committee approval.

Premature study end or interruption of the study will be reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

2.4 Competent Authorities (CA)

The protocol of this trial will be submitted to the ethical committees (EC) of the Nordwest and Zentralschweiz (Leitethikkommission) and additional approval will be sought from all remaining ECs in Switzerland. Since this trial is conducted within routine care there are no further authorities involved.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, in case of medical device: the European Directive on medical devices 93/42/EEC and the ISO Norm 14155 and ISO 14971, the Swiss Law and Swiss regulatory authority's requirements.

All staff involved in the pragmatic trial will have to fulfil requirements in regard to training, data management and data analysis as set by the Swiss National Science Foundation.

Writing of protocol and final manuscripts will be in adherence with reporting standards of SPIRIT, CONSORT and RECORD.[1-3]

2.6 Declaration of interest

This is an investigator-initiated trial conducted entirely with public support by the Swiss National Science Foundation within the "Nationale Forschungsprogramm 'Antimikrobielle Resistenz' (NFP 72)" (www.nfp72.ch).

The sponsor of the trial is the University Hospital Basel.

2.7 Patient Information and Informed Consent

Physicians in the intervention group will not have to provide informed consent but they may opt out of participating to the trial at any time and decline receiving any of the information letters. Opting out will be possible by mail, phone, through the online service or by returning an anonymized, stamped response postcard which will have been sent to the physicians with the first feedback package. Physicians in the control group will not be notified and receive no material.

Investigators will take any measures to guarantee the confidentiality of all collected

data as the data provided by health insurers will be anonymized.

2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

Ethics committees have guaranteed access to all original and processed data and permission to audit the project at any time (access to non-anonymized data must be authorized by CSS, Helsana, and Sanitas due to Swiss data protection law).

2.9 Early termination of the study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, for example ethical concerns or early evidence of harm of the experimental intervention.

2.10 Protocol amendments

Substantial amendments are only implemented after approval of the CEC.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC. Such deviations shall be documented and reported to the sponsor and the CEC as soon as possible.

A formal amendment to the protocol will be made for issues that may impact the conduct of the study or affect patient’s benefit or harm. This includes particularity substantive changes of the objectives, design, eligibility criteria, sample size, and duration of follow up. Such major amendments will be agreed upon by the ombudsman (guardian, see 1.7) and the study investigators and approved by the ethics committee prior to implementation.

Minor changes that have no effect on the study conduct of primarily administrative nature will be documented in a memorandum. The investigators will inform the Ethics Committee about such minor at their discretion. All changes will be documented in the final results publication of the study.

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Antibiotic resistance is an increasingly serious problem worldwide but also in Europe and Switzerland[4]. In many countries, resistance rates have more than doubled in the past five years[5]. The emergence of antibiotic resistance is associated with the increasing exposure and overall uptake of antibiotics in a population[6]. Experience from several European countries shows that reduced antibiotic prescribing for outpatients is paralleled by a decrease in antibiotic resistance rates for most antibiotic classes.[7].

In Europe, 80% to 90% of antibiotics are used in primary care and the most frequent reasons for antibiotic prescribing are acute upper and lower respiratory tract infections (ARTI)[8-10], although primarily of viral origin, and urinary tract infections[11]. Outpatient antibiotic use in Switzerland is relatively low compared to other European countries, but there is considerable variation in prescription rates between Swiss regions with a relatively high use of macrolides and fluoroquinolones, a known risk factor for antibiotic resistance, in particular for *S. pneumoniae*[12].

To lower antibiotic prescriptions new strategies must be implemented that involve the '*4 P main stakeholders'*, prescribers, patients, payers and public health epidemiologists. Multiple approaches of stewardship programs to lower antibiotic use in primary care have been investigated using observational designs, typically before/after studies, or randomized trials. Interventions include provider or patient information tools, provision of treatment guidelines, communication training, delayed prescriptions and point of care testing.

A recent Health Technology Assessment from the United States found only low to moderate quality evidence on the effectiveness of these interventions due to insufficient study designs and inconsistent intervention effects[13]. Most studies selected a relatively small number of practices with motivated practitioners, and were too short to assess long-term effects on antibiotic prescription rates. Only few studies reported whether reduction in antibiotic prescriptions was safe and not associated with negative impact on patient relevant outcomes. Long term consequences of the interventions were insufficiently addressed and no study addressed the consequences of the intervention on antibiotic resistance. Trials on face-to-face provider education and academic detailing showed a more consistent reduction in overall antibiotic prescribing of 4% and about 3% per year and 1000 registered patients[14,15]. These interventions, however, are resource intense and therefore most likely not sustainable when applied at a large scale.

3.2 Investigational Product (treatment, device) and Indication

The investigated intervention is a nationwide intervention within the framework of the Swiss National Science Foundation program 72 on 'Antimicrobial Resistance' combining routine prescription and antibiotic resistance feedback in addition to the provision of evidence-based physician and patient education material. For details see Section 8.1.1.

3.3 Preclinical Evidence

Not applicable.

3.4 Clinical Evidence to Date

We have conducted a *systematic review* to identify all randomized controlled trials

(RCTs) investigating the effectiveness of routine monitoring and prescription feedback to lower antibiotic prescriptions in primary care. We searched for RCTs, including cluster RCTs, evaluating antibiotic prescription feedback interventions in primary care which are implementable on a system level, i.e. not involving direct physician contact, and without combined patient directed interventions. We searched PubMed from inception to 2016 for systematic reviews on antibiotic prescription feedback interventions. The two most recent relevant reviews were perused for eligible RCTs. For the time-period not covered by these reviews, we directly queried PubMed for RCTs (i.e. from 1 January 2012 to 14 April 2016). We combined MeSH headings and text terms for "antibiotics" and "feedback" and used the PubMed standard filter for systematic reviews and a Cochrane standard filter for RCTs.

There are three large-scale trials evaluating feedback interventions. One found no impact on antibiotic prescriptions when two mailed feedbacks, that addressed antibiotic prescribing and prescribing of four other drug groups, were given in 1995 to unselected Australian general practitioners[16]. The second found that a single feedback letter sent to the top 20% antibiotic prescribing general practitioners in 2014 in England reduced antibiotic prescribing by 3.3% over 6 months[17].

The third and largest trial in this field has recently been completed by our group[18]. We have conducted a nationwide pragmatic trial on quarterly personalized prescription feedback to reduce antibiotic overuse in primary care (ClinicalTrials.gov identifier: NCT01773824). We randomized the 2900 primary care physicians in Switzerland with the highest antibiotics prescription rates (median of 100.6 defined daily doses (DDD) antibiotics per 100 consultations in the year before the study). Physicians in the intervention group received quarterly personalized prescription feedback by mail and were provided with secured web-based access to analyses of their individual prescription data. We used routinely collected administrative claims data of SASIS/Santésuisse.

We found that the intervention may reduce prescriptions to older children and adolescents aged 6 to 18 years (-8·6% in the first year; 95%CI -14.8% to -1.9%) and younger adults (-4.6%; -7.9% to -1.2% in the second year). but not in the population at large (first year 0.8%; 2.6% to 4.3%; second year 1.7%; -5.1% to 1.7%). In addition we noted no shift towards less use of broad spectrum antibiotics. Data collection for this trial ended December 31, 2015. These findings underline the feasibility of such feedback, but we need a better understanding of the effects on patient-relevant outcomes, on antibiotic resistance, and of the underlying mechanisms leading to different effects in certain subgroups of patients before routine implementation in the Swiss health care system.

3.5 Dose Rationale / Medical Device: Rationale for the intended purpose in study (pre-market MD)

Not applicable.

3.6 Explanation for choice of comparator (or placebo)

The control intervention is the usual care in Switzerland without any changes of routine care. Thus, no intervention will be provided to the comparator group and they will not be contacted in any way. The prescription behavior of the physician in the control group will also be evaluated entirely anonymously.

3.7 Risks / Benefits

The intervention does not pose any harm to a patient as no contact with them will be

made, only educational information that is in agreement with best current evidence of patient information and that has been reviewed by several national and international experts in the field will be provided. The patient and physician data will be anonymized.

Any theoretical risk of the evaluated program would be similar to other feedback on prescribing as provided routinely for financial or economic reasons. The informed consent process in clinical trials should be tailored to the raised ethical concerns; hence we believe that patients need not to be informed of this trial without any breech in ethical standards[19].

We also believe that in this special type of pragmatic study a disclosure of the random sampling and randomized analysis is not required because the situation is different to that of traditional clinical trials since the risks associated with the receipt of an evidence-based, guideline concordant treatment are only of theoretical nature and would be below the variability of treatment provided during the standard care. The randomization in the trial's arm does not pose an inherently higher risk than the care based on the physician's judgment.

As far as data protection is concern, extreme efforts and a strict use of anonymous identifiers will be placed in protecting the confidentiality of this data and any potentially associated privacy risk is so meager that informing the patients is not deemed necessary.

Furthermore, informing the physician or patient and making them aware of being "monitored" may introduce Hawthorne's effects not letting us to clearly evaluate if such a nationwide quality improvement program would work. This would decrease the usefulness of the trial, limit the applicability of its results by reducing the external validity and thus, reducing the benefits of this national program.

3.8 Justification of choice of study population

In Europe, 80% to 90% of antibiotics are used in primary care, thus this population is the most relevant target for initiative aiming to reduce antibiotic consumption.

We address the stewardship program to a random sample of the top 75% antibiotic prescribers since we believe that the public health impact and the problem of antibiotic overtreatment is low in the lowest quartile of primary care physicians.

4. STUDY OBJECTIVES

4.1 Overall Objective

To evaluate a nationwide intervention program combining routine prescription and resistance feedback with the provision of evidence-based physician and patient education material within a large-scale pragmatic randomized controlled trial in primary care physicians in Switzerland.

4.2 Primary Objective

To evaluate whether this program reduces the total amount of antibiotics prescribed over a longer period, i.e. after 13 to 24 months (longer term intervention effect, second year of the study).

4.3 Secondary Objectives

To specifically explore the impact of this program on specific patient-populations defined by age groups, on prescribing of specific types of antibiotics, on patient relevant outcomes (i.e. hospitalizations), and costs.

4.4 Safety Objectives

There are no specific safety objectives to be considered for this study.

5. STUDY OUTCOMES

5.1 Primary Outcome

The *primary outcome* of the trial is the overall antibiotic use, defined as prescribed defined daily doses (DDD) of antibiotics per 100 patient consultations (total patient population) evaluated over a period of 12 months, from month 13 to month 24 post randomization (longer term intervention effect).

5.2 Secondary Outcomes

The *secondary outcomes* are:

- **(1)** Overall antibiotic use defined as prescribed defined daily doses (DDD) of antibiotics per 100 patient consultations evaluated over a period of 12 months, from month 1 to month 12 post randomization (short-term intervention effect);
- **(2)** Overall antibiotic use defined as prescribed defined daily doses (DDD) of antibiotics per 100 patient consultations evaluated over a period of 24 months, from month 1 to month 24 post randomization, with two repeated measurements, over the first and the second 12 month period post
- **(3)** Use of broad spectrum antibiotics in the total patient population (DDD of this specific type per 100 consultations)
    a. quinolones
    b. oral cephalosporines ;
- **(4)** Hospitalizations annual rates, defined over the period of interest as the number of patients with at least one hospitalization over the total number of patients with at least one consultation over the same period, and specifically evaluated for each physician., for the following two reasons
    a. all-cause
    b. related to infections (DRG-based)
- **(5)** Antibiotic use (DDD per 100 consultations) in four specific age groups, in patients
    a. <6,
    b. 6 to <18,
    c. 18 to <65,
    d. ≥ 65 years);

Secondary outcomes (3) to (6) will be evaluated over two 12 month periods, from month 1 to month 12, and from month 13 to month 24.

5.3 Other Outcomes of Interest

We will exploratively evaluate the specific use of macrolides, tetracyclines, aminopenicillins & amoxicillin with and without clavulanate over the first (month 1 to month 12) and second year (month 13 to month 24 after randomization). We will evaluate the costs, including costs of antibiotics, related outpatient costs, costs of hospitalizations due to infection, costs per patient with identifiable infection; overall charges of participating physicians (per consultation and per patient, across all patients) and the costs of the program.

5.4 Safety Outcomes

There are no safety outcomes.

6. STUDY DESIGN

6.1 General study design and justification of design

This is a pragmatic randomized, superiority, parallel group design trial with 2:1 randomization ratio in primary care physicians in Switzerland with normal and high antibiotic prescription rates (i.e. among top 75% antibiotic prescribers). The trial is based on routinely collected individual reimbursement claims data of the three largest Swiss health insurers and on routinely collected surveillance data on antibiotic resistance. Unit of analysis and randomization is the physician.

6.2 Methods of minimizing bias

6.2.1 Randomization

Selected physicians will be randomized (simple randomization) in September 2017 in a 2:1 ratio to the intervention or control, using a computer-generated algorithm by a biostatistician who is not further involved in the trial. Allocation concealment is perfect due to the central enrollment and randomization in one step (not consecutive).

6.2.2 Blinding procedures

Physicians are formally blinded (they will not be contacted if in the control group, and unaware of the fact that this study has a randomized design with an intervention and control group).

The outcome assessment is formally blinded due to the nature of the routinely collected data (all data is collected not for the purpose of this study).

6.2.3 Other methods of minimizing bias

Physicians in the intervention group are not required to provide informed consent, but they may opt out and decline receiving any of the interventional information. Physicians in the control group will not be notified. This design maximizes the external validity and applicability of the findings and minimizes numerous biases, including the avoidance of a Hawthorne effect, i.e. behavioral changes not caused by the invention but introduced by the fact that study participants know that they are being observed. Contamination due to crossing-over effects from the core components of the intervention is almost impossible due to the centralized provision of the personalized feedback without opportunity to be shared between groups.

6.3 Unblinding Procedures (Code break)

Unblinding will be done when the final dataset has been provided for analysis.

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7. STUDY POPULATION

This is a nationwide study enrolling a large proportion (in the range of 70% to 75%) of all registered primary care physicians (general internal medicine and pediatrics and adolescence medicine) treating patients insured by the three largest Swiss statutory health insurers, in an estimated number of 3.8 million Swiss residents.

7.1 Eligibility criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Primary care physician in Switzerland (FMH general internal medicine or pediatrics and adolescence medicine)
- Above the 25th percentile of antibiotic prescribers (i.e. within the upper three quarters of antibiotic prescribers, with prescriptions defined as DDD/100 consultations)
- Consulting with at least 100 patients per year
- With individual Zahlstellenregister (ZSR) number.

The ZSR-number (an unique physician identifier number used for reimbursement and surveillance purposes by Santésuisse, the umbrella organization of all Swiss health insurers) in the database of health insurers. Physicians with shared, non-individual numbers, for example in hospitals, are not eligible.

7.2 Recruitment and screening

All physicians meeting the eligibility criteria will be identified based on reimbursement claims data over a 12-month time period preceding the randomization. A random sample of physicians will be selected for randomization.

7.3 Assignment to study groups

Selected physicians will be randomized to the intervention or control group.

7.4 Criteria for withdrawal / discontinuation of participants

Physicians in the intervention group may opt out from the trial at any stage by mail, phone, through the online service or by returning an anonymized, stamped response postcard which will have been sent to the physicians with the first feedback package.

They will not receive any further study material but will not be considered drop-outs and their follow-up data will remain in the intention-to-treat analysis. Physicians withdrawing from clinical practice (e.g. closing practice or retiring) remain in the study until the ZRS number is discarded.

8. STUDY INTERVENTION

8.1 Identity of Investigational Products (treatment / medical device)

8.1.1 Experimental Intervention (treatment / medical device)

The intervention is a combined antibiotic stewardship program that has two core elements, prescription feedback and antibiotic resistance data feedback, and two supporting educational elements targeting physicians and patients. The former will be provided continuously and quarterly, while the latter are provided only once. The intervention period will be 24 months.

A: Routinely provided continuous personalized prescription feedback to prescribers by postal mail and online services

Feedback information will be sent every three months in form of a letter including a condensed graphical overview (single page, see Appendix 1) of the most important information. We plan to show the individual amount of antibiotic prescriptions (in defined daily doses, DDD) per 100 consultations in the preceding months and display the updated and adjusted average in peer physicians (using a population-based linear regression model including adjustments for e.g. geographic region and patient-mix, i.e. age groups, sex, and comorbidities of patients).

The feedback will also include the number of prescribed packages, individually used antibiotic types and antibiotic resistance data from the community and served patient population.

Appropriate methods for feedback to pediatricians will be explored and implemented (e.g. specific display of prescribed packages in children).

Physicians will be invited to visit the study website via personalized access codes to receive further detailed information There more detailed feedback information will be provided via a secured online service (the individual access codes are sent via postal mail). This will include interactive presentations of the amount of antibiotic prescriptions by type of antibiotics, age groups, sex and other patient groups (e.g. defined by comorbidities). The web-application has been developed by us and pilot-tested in the previous trial.

The data included in the feedback will be anonymized. We will use anonymous physician identifiers and only aggregated patient-related information is included in the feedback (for example prescription rates in age-groups).

B: Educational material

We will provide once educational material targeting physicians (evidence-based guidelines for conditions leading to most outpatient prescriptions in primary care) and patients (validated information material on using antibiotics wisely).

Evidence-based guidelines, updated and adapted for the Swiss health care context and peer-reviewed by national experts in the field (including general practitioners, pediatricians, ENT-specialists, epidemiologic and infectiologists) for the management of acute respiratory tract infections and uncomplicated urinary tract infections developed in a previous trial will be provided as paper brochure with the first mailing all physicians in the intervention group.

In addition, physicians in the intervention group will receive leaflets and posters to be displayed in waiting areas of practices informing patients about

the problems of inappropriate antibiotic use. All material will be pilot tested in practices and structured feedback from primary care physicians and their patients will be obtained.

We will provide all information in the three official languages in Switzerland, German, French, and Italian. For feasibility and cost reasons, the treatment guidelines are provided only as German and French version, because more than 90% of physicians' offices are located in the German and French speaking regions of Switzerland.

8.1.2 Control Intervention (standard/routine/comparator treatment / medical device)

Usual Care. Physicians in the control group receive no intervention or material. However, their anonymous prescription data is obtained and analyzed.

8.1.3 Packaging, Labelling and Supply (re-supply)

Not applicable

8.1.4 Storage Conditions

Not applicable

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

Not applicable

8.2.2 Control Intervention

Not applicable

8.3 Dose / Device modifications

Not applicable.

8.4 Compliance with study intervention

Not applicable.

8.5 Data Collection and Follow-up for withdrawn participants

The routinely collected health data in this study are used to identify the eligible physicians, provide the feedback on antibiotic prescriptions, and measure the outcomes. These data will be provided by the health insurers as standardized and continuously updated datasets containing all study-relevant information. The baseline data will contain the relevant variables for a 12-month period preceding the randomization. Datasets for the prescription feedback information are quarterly updated, and the first provision will be in September 2017.

Each dataset will include the most recent information for each physician included into the trial with a unique anonymous physician identifier (based on the ZSR number) uniformly provided by all three health insurers. All patients with any consultation during the trial period will be linked to the physician identifier by a unique anonymous patient identifier that will allow tracking all patients who had consultations with their primary care physician.

The trial database will contain the following data: number and dates of consultations, age and sex of consulting patients, prescriptions of antibiotics coded by ATC (Anatomical Therapeutic Chemical Classification-System) and date of prescription redemption, prescriptions of non-antibiotic co-medications coded by “pharmacy cost groups” (PCG, a Swiss drug classification system based on ATC codes allowing to identify 10 majors disease categories), dates and types of ambulatory laboratory tests with unique laboratory identification number (blood count, C-reactive protein, urine dipstick, urine culture, pharyngeal swab, PCR-tests for respiratory viruses), date of chest X-ray, dates of any consultations to emergency departments, ambulatories or walk-in clinics (‘Permanences’) and dates of prescribed antibiotics during such consultations, any hospitalization (with DRGs), costs for all patients with antibiotic prescriptions and hospitalization due to infections or other reasons in any patient (irrespective of the receipt of an antibiotic prescription).

Antibiotics will be identified by their ATC code, and the identification of the specific drug, application form, doses and package size will be done using the swiss Spezialitätenliste.

8.6 Trial specific preventive measures

Not applicable.

8.7 Concomitant Interventions (treatments)

Not applicable.

8.8 Study Drug / Medical Device Accountability

Not applicable.

8.9 Return or Destruction of Study Drug / Medical Device

Not applicable.

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments

Routinely collected health data is used to identify eligible physicians, provide feedback on antibiotic prescriptions, and measure the study outcomes. These data will be provided by health insurers and will be continuously updated over the course of the study.

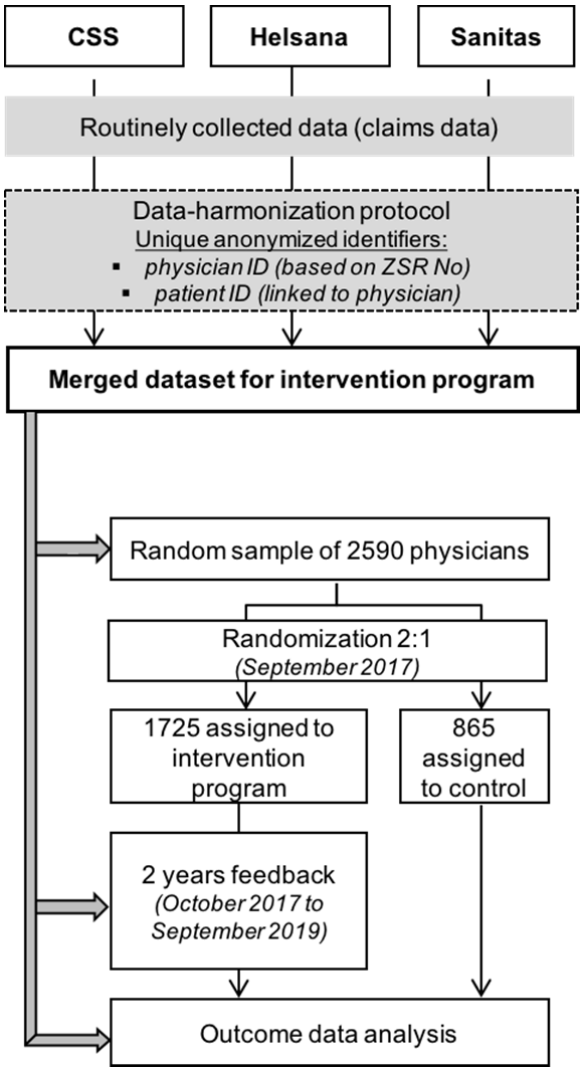
To identify eligible participants, the insurance companies (CSS, Helsana, Sanitas) will create a list, using anonymous physician identifiers, of board certified primary care physicians with FMH title in general internal medicine or paediatrics and adolescent medicine, having an individual Zahlstellenregister number and consulting with more than 100 patients in the baseline period.

For each potentially eligible physician, the number of prescriptions of antibiotics per patient will be determined and the top 75% of prescribers will be used as eligible participant population. From these physicians, a random sample of 2590 will be selected as the study population.

For all included physicians, an extended dataset with additional variables will be provided by health insurers starting from 12-month preceding study randomization. Datasets for the prescription feedback information are quarterly updated over the course of the study (see Study Flow Chart).

Each dataset will include the most up to date information for each physician included into the trial with a unique anonymous physician identifier, uniformly provided by all three health insurers. For patients with consultations to these physicians (using a unique anonymous patient identifier per insurance company), information on their age group (in 5 years) and sex will be included together with reimbursement data on (1) consultations, (2) prescriptions of antibiotics (coded by ATC, Anatomical Therapeutic Chemical Classification-System), (3) grouped information on prescriptions of non-antibiotic co-medications (“pharmacy cost groups”, PCG, a Swiss drug classification system based on ATC codes allowing to identify 10 majors disease categories), reimbursed diagnostics tests (blood count, C-reactive protein, urine dipstick, urine culture, pharyngeal swab, PCR-tests for respiratory viruses, chest X-ray), consultations to emergency departments, ambulatories or walk-in clinics (‘Permanences’), and Hospitalizations (Swiss-DRG Codes). Details about the data structure including operationalization of the outcomes and details about database linkage will be specifically defined in a routine data analysis plan developed in collaboration with the data managers of the participating insurance companies.

744 **Study Flow Chart**



745
746

9.2 Assessments of outcomes

All outcomes are measured using the routinely collected insurance claims data.

Study timetable

Task & Month (planned start 09/2017)	1	2	5	8	11	14	17	20	23	29
Selection and randomization (September 2017)	**x**									
Provision of feedback by postal mail		x	x	x	x	x	x	x	x	
Provision of online service		x	x	x	x	x	x	x	x	
Transfer and provision of routine data by health insurers	x	x	x	x	x	x	x	x	x	x
Start of main data analysis										x

9.2.1 Assessment of primary outcome

Please refer to Section 9.1.

9.2.2 Assessment of secondary outcomes

Please refer to Section 9.1.

9.2.3 Assessment of other outcomes of interest

Not applicable.

9.2.4 Assessment of safety outcomes

Not applicable.

9.2.5 Assessments in participants who prematurely stop the study

Not applicable.

9.3 Procedures at each visit

Not applicable.

10. SAFETY

This trial will not utilize any pharmaceutical component, medical device or transplant material and no individual patient outcomes or adverse events will be measurable; hence, no safety measures are described.

11. STATISTICAL METHODS

11.1 Hypothesis

The statistical hypothesis to test is

H_0: $\mu_1 = \mu_0$ versus H_1: $\mu_1 \neq \mu_0$

where μ_1 is the population mean of the reduction (change score) in prescribed defined daily doses (DDD) of antibiotics per 100 patient consultations in the intervention arm and μ_0 is the population mean of the reduction in the control arm (primary outcome, as defined in Section 5.1).

The null hypothesis H_0 will be tested against the alternative H_1 using ANCOVA.

11.2 Determination of Sample Size

We used historic monthly aggregated outpatient data from SASIS used in our previous trial to calculate the required sample size using resampling methods (bootstrapping). We aim to detect a minimum reduction of total antibiotic prescriptions by 5% in the intention to treat population with a statistical power of 90%. We deem this 5% reduction of antibiotic prescriptions a minimally public health relevant effect on a nationwide level in Switzerland. This corresponds to 3.5 DDD per 100 consultations prescribed less per year in the intervention group as compared to the control. The median prescription rate of antibiotics in primary care physicians in Switzerland is estimated to be 70 DDD/100 consultations. Based on data from our previous trial, we assume that there will be physicians who opt out from the intervention (in a range of 15%) and physicians who will not change their prescription behavior. Based on these assumptions and using an intention to treat approach, we will randomize 2590 physicians in a 2:1 ratio to the intervention (n=1725) and control group (n=865). We plan to use an unequal allocation ratio to direct the intervention to a large proportion of the final target physician population From a pragmatic trial perspective this approach appears reasonable given the low additional costs for recruitment, intervention, and outcome measurement. The main concern of unbalanced allocation is efficiency which may lead to a small loss of statistical power, which we have accounted for. There is a large variability of prescribing rates across physicians in this former dataset, and much of this is explained by group practices (i.e. physicians sharing ZSR numbers) which will be excluded in the current study. Therefore, the sample size calculation is a conservative estimate.

11.3 Statistical criteria of termination of trial

Not applicable.

11.4 Planned Analyses

11.4.1 Datasets to be analysed, analysis populations

All analyses will be conducted using the final dataset. The analysis population is all randomized physicians. All analyses will be based on the intention-to-treat principle, i.e. all participants will be analyzed in the group to which they are randomized.

We plan to evaluate all outcomes exploratively in the subgroup of physicians who are among the top 25% prescribers in Switzerland. No other subgroups are prespecified.

11.4.2 Primary Analysis

The effect on the primary outcome will be assessed by comparing the mean change from baseline in prescribed DDD of antibiotics per 100 patient consultations over month 13 to month 24 post randomization (primary outcome, see Section 5.1). The comparison will be performed by using ANCOVA modelling, with the outcome as response, intervention (yes/no) as factor of interest and baseline value as a covariate. Log-transformation may be applied. Other baseline covariates of interest include hospitalizations due to infection in the 12-month period preceding the randomization and comorbidities based on pharmacy cost groups. The baseline covariates will be selected prior to un-blinding of the treatment allocation. Coefficient estimates and their 95% CI will be reported.

All analyses will be performed by the lead trial statistician after provision of the final dataset from the health insurers. Analyses will be performed using SAS and R software.

11.4.3 Secondary Analyses

(1) The analysis for the secondary outcome (1) in Section 5.2 will be a repetition of the primary analysis for the first 12 months post randomization, where the difference between the intervention and the control arm will be again assessed by ANCOVA modelling.

(2) For outcome (2) in Section 5.2 the log-transformed prescribed DDD per 100 consultations will be modelled via a linear mixed model on the intervention (yes/no), and including time (baseline, first year, second year) and the interaction of intervention with time. Physician random effects on the intercept and the slope will be considered. The intervention effect will be evaluated by comparing the intervention and control group. Mean percentage changes from baseline will be derived for the intervention and control groups. Other baseline covariates of interest will be included as for the primary analysis, and log-transformation may be applied. Coefficient estimates and their 95% CI will be reported.

(3) The analysis of outcome (3) in Section 5.2 will be a repetition of the primary analysis for two time periods, the first year post-randomization and the second year post-randomization, separately for DDD per 100 consultation of quinolones and oral cephalosporines.

(4) The rates of hospitalizations corresponding to outcomes (4a) and (4b) in Section 5.2 will be modelled by means of logistic regressions including the intervention as factor of interest and other relevant covariates. Hospitalization rates in the intervention and control goup, with exact 95% confidence intervals will be reported, and odds ratios for the intervention arm vs control will be derived from the coefficients estimated for the logistic regression model.

(5) The analysis for outcome (5) in Section 5.2 is a repetition of the primary analysis separately over two time periods (first and second year post-

randomization) and over the following subgroups (or stratified analysis)

a. <6,
b. 6 to <18,
c. 18 to <65,
d. >= 65 years);

All analyses will be done by the lead trial statistician after provision of the final dataset from the health insurers. Analyses will be performed using SAS and R software

11.4.4 Interim analyses

No interim analyses are planned.

11.4.5 Safety analysis

No safety analyses are planned.

11.4.6 Deviation(s) from the original statistical plan

Any relevant deviation from the original statistical plan will be reported and explained in the published study report.

11.5 Handling of missing data and drop-outs

We expect a low amount of missing data resulting from drop-outs (based on experience with our previous trial in a range of 3%) and assume that the underlying reasons for missing data (such as discarded ZSR-numbers due to physician retirement) is completely at random. Thus we exclude these physicians from our analyses without risking biased results.

12. QUALITY ASSURANCE AND CONTROL

12.1 Data handling and record keeping / archiving

All data provided by health insurers will be anonymized to ensure confidentiality of records that could identify individual physicians and their patients. The coordinating data manager from Sanitas will use the ZSR numbers (which are centrally distributed and provided for all physicians with licenses in Switzerland by SASIS/Santésuisse) to generate unique anonymous identifiers for all included physicians.

A unique patient identifier will be used by the health insurers for the analysis of anonymized claims data per physician, but this identifier will not be released to the study investigators or the study staff at any time. This trial will not involve or directly collect any prospective data from individual patients. The set-up for data collection and the appropriate anonymization of data is of outmost importance to comply with data protection rules.

The study investigators must not know which data comes from which insurer. To ensure that the insurers are not identifiable, an independent data center which is not part of the study group and not part of the insurers will act as intermediate data operator and receive the insurance data and provide them to the investigators without any variable or marker allowing to identify the insurer. The Clinical Trial Unit University Hospital Basel will act in this function, applying all established rules of data protection and anonymization. The specified study datasets will be securely transferred in encrypted format from health insurers to the intermediate data operator who will then (after anonymizing the insurers) transfer the data to the study center at Basel Institute for Clinical Epidemiology & Biostatistics (CEB), University Hospital Basel.

All randomized study participants will be marked with an anonymous identifier. An encrypted list of all identifiers will be generated by each insurer and kept secure on a dedicated network directory for at least 10 years. The encryption will be done via AES-256 symmetric encryption of archive files. Respective passwords will be kept separate from the data.

All study data will be stored and processed on infrastructure located within the University Hospital Basel and data management will be conducted in accordance to the procedures used for trial data management by the clinical trial unit. Access to the dataset will be strictly limited to the data manager and the biostatistician of the project. To provide participants with additional information, a condensed dataset will be generated for the study website and stored on a server hosted by nine.ch.

All data may only be used for the study purpose. A contract between the principle investigator and health insurers will be set-up to regulate all issues of data protection and data rights. All staff of CEB involved in the trial and the director of the Institute will sign a confidentially form.

Postal-addresses of physicians are included in records of the health insurers. Postal anonymized feedback forms will be generated through an automated process by CEB and packing of the envelopes will be centrally executed, maintaining anonymity of randomized physicians.

The password protected webpage for the trial for intervention support material and guidelines will be hosted by nine.ch, a dedicated hosting company in Zurich. A virtual server and separate off-site backup will be rented for the study duration, allowing expansion of storage and computing capacity in case of need (https://www.nine.ch/de/root/vserver/). The trial website and respective database,

server and backup systems will be managed by Saccilotto Consulting, Basel, Switzerland.

12.1.1 Case Report Forms

All study data is collected in routine care and no specific CRFs are created.

12.1.2 Specification of source documents

Not applicable.

12.1.3 Record keeping / archiving

All study data will be archived for a minimum of 10 years after study termination or premature termination of the pragmatic trial.

12.2 Data management

Data management procedures will be detailed in collaboration with the health insurance providers as respective study standard operating procedures.

12.2.1 Data Management System

Health insurers will use their own data management systems to collect and process the data. The study data managers will use a relational database system in combination with custom developed programs to manage the data. All processes will be tested with dummy data before the start of the study and random samples will be manually checked as part of the quality assurance process.

12.2.2 Data security, access and back-up

Access to the data will be physically limited to study personnel and only data manager and biostatistician of the study will be given access-codes to the data.

The condensed data used for the study website will only be accessible to the study data-manager and will be stored on a webserver hosted by nine.ch

12.2.3 Analysis and archiving

At the end of the study all raw data, processing algorithms and analyses code will be transferred in duplicate to optical storage mediums (DVDs) and will be securely archived at the Basel Institute for Clinical Epidemiology & Biostatistics (CEB).

12.2.4 Electronic and central data validation

No data used in this study is collected for the purpose of research; therefore there is no specific data validation process. All data is collected by health insurers during routine care in usual practice.

12.3 Monitoring

No data used in this study is collected for the purpose of research; therefore there is no specific data monitoring process. Please also see Section 1.7.

12.4 Audits and Inspections

Not applicable.

12.5 Confidentiality, Data Protection

See Section 12.1.

12.6 Storage of biological material and related health data

The data will be stored on a dedicated physical machine and respective backup devices without internet connectivity located at the Basel Institute for Clinical Epidemiology & Biostatistic. The condensed website data will be stored on a server in Zurich, Switzerland hosted by nine.ch.

13. PUBLICATION AND DISSEMINATION POLICY

All trials results will be published with open access in peer-reviewed journal publications. After completion of the study a summary of the results will be send to all included general participants.

14. FUNDING AND SUPPORT

14.1 Funding

This study is funded by a grant from the Swiss National Science Foundation (NFP 72 – Grant No NMS1927) The funding for this trial is provided by the Swiss National Science Foundation (SNSF). The insurance data is provided by CSS, Helsana, and Sanitas, free of charge.

14.2 Other Support

The three largest Swiss health insurers, CSS, Helsana, and Sanitas will be providing the insurance data for this trial. They will contribute with their database and assist in the successful merging and handling of this data to our research team.

The Swiss Medical Association (FMH, Berne), the official association of Swiss physicians, will provide official support of the intervention program to increase impact.

Swissnoso, the national reference center for infection prevention will provide expertise in antibiotic stewardship programs, support with scientific expertise the guideline development, and is official supporter of the intervention program to increase impact.

Partners are summarized in Section 1.8.

15. INSURANCE

Insurance will be provided by the Sponsor, the University Hospital Basel.

A copy of the certificate is filed in the central investigator site file and the trial master file.

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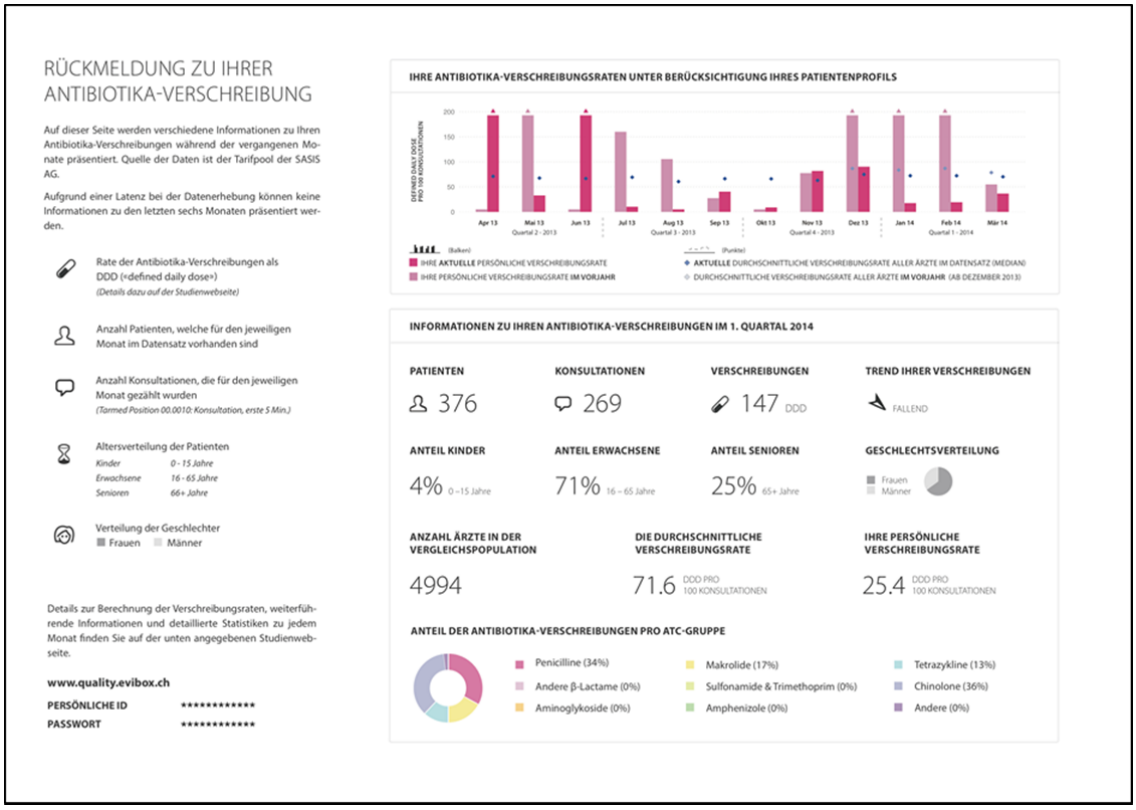
17. APPENDIX

Appendix 1: Example of the intervention material: Prescription feedback to physicians



RÜCKMELDUNG ZU IHRER ANTIBIOTIKA-VERSCHREIBUNG

Auf dieser Seite werden verschiedene Informationen zu Ihren Antibiotika-Verschreibungen während der vergangenen Monate präsentiert. Quelle der Daten ist der Tarifpool der SASIS AG.

Aufgrund einer Latenz bei der Datenerhebung können keine Informationen zu den letzten sechs Monaten präsentiert werden.

Rate der Antibiotika-Verschreibungen als DDD («defined daily dose»)
(Details dazu auf der Studienwebseite)

Anzahl Patienten, welche für den jeweiligen Monat im Datensatz vorhanden sind

Anzahl Konsultationen, die für den jeweiligen Monat gezählt wurden
(Tarmed Position 00.0010: Konsultation, erste 5 Min.)

Altersverteilung der Patienten
Kinder *0 - 15 Jahre*
Erwachsene *16 - 65 Jahre*
Senioren *66+ Jahre*

Verteilung der Geschlechter
Frauen Männer

Details zur Berechnung der Verschreibungsraten, weiterführende Informationen und detaillierte Statistiken zu jedem Monat finden Sie auf der unten angegebenen Studienwebseite.

www.quality.evibox.ch

PERSÖNLICHE ID **********
PASSWORT **********

IHRE ANTIBIOTIKA-VERSCHREIBUNGSRATEN UNTER BERÜCKSICHTIGUNG IHRES PATIENTENPROFILS

INFORMATIONEN ZU IHREN ANTIBIOTIKA-VERSCHREIBUNGEN IM 1. QUARTAL 2014

PATIENTEN	KONSULTATIONEN	VERSCHREIBUNGEN	TREND IHRER VERSCHREIBUNGEN
376	269	147 DDD	FALLEND

ANTEIL KINDER	ANTEIL ERWACHSENE	ANTEIL SENIOREN	GESCHLECHTSVERTEILUNG
4% 0 – 15 Jahre	71% 16 – 65 Jahre	25% 65+ Jahre	Frauen Männer

ANZAHL ÄRZTE IN DER VERGLEICHSPOPULATION	DIE DURCHSCHNITTLICHE VERSCHREIBUNGSRATE	IHRE PERSÖNLICHE VERSCHREIBUNGSRATE
4994	71.6 DDD PRO 100 KONSULTATIONEN	25.4 DDD PRO 100 KONSULTATIONEN

ANTEIL DER ANTIBIOTIKA-VERSCHREIBUNGEN PRO ATC-GRUPPE

Universitätsspital Basel

Klinische Epidemiologie

Prüfplan/Protokoll HFV: Weiterverwendung biologischen Materials und/oder gesundheitsbezogener Personendaten für die Forschung bei fehlender Einwilligung und Information nach Artikel 34 HFG

Title

Routine antibiotic prescription and resistance feedback in primary care: A nationwide pragmatic randomized controlled trial

Project leader

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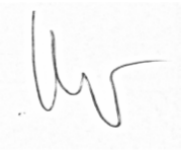
Confirmation

By submitting my signature, I confirm that all the data contained in this action plan are correct and I am committed to respecting the data provided and national legislation, in particular regarding data protection.



Basel, April 2nd 2020

Abbreviations

4P	Prescribers, patients, payers and public health epidemiologists
AE	Adverse Event
ARTI	Acute upper and lower respiratory tract infections
ATC	Anatomical Therapeutic Chemical Classification System
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CRF	Case Report Form
ClinO	Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin)
DRG	Diagnosis-related group
eCRF	Electronic Case Report Form
FMH	Foederatio Medicorum Helveticorum
GCP	Good Clinical Practice
IB	Investigator's Brochure
H_o	Null hypothesis
H_1	Alternative hypothesis
HFG	Humanforschungsgesetz (Law on human research)
IMP	Investigational Medicinal Product
ISO	International Organisation for Standardisation
ITT	Intention to treat
KlinV	Verordnung über klinische Versuche in der Humanforschung (in English: ClinO, in French OClin)
MD	Medical Device
OClin	Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain (in German : KlinV, in English : ClinO)
PI	Principal Investigator
RCT	Randomized controlled trial
SOP	Standard Operating Procedure
SPC	Summary of product characteristics
ZSR	Zahlstellenregister

Background

Antibiotic resistance is an increasingly serious problem worldwide but also in Europe and Switzerland[1]. In many countries, resistance rates have more than doubled in the past five years[2]. The emergence of antibiotic resistance is associated with the increasing exposure and overall uptake of antibiotics in a population[3]. Experience from several European countries shows that reduced antibiotic prescribing for outpatients is paralleled by a decrease in antibiotic resistance rates for most antibiotic classes[4].

In Europe, 80% to 90% of antibiotics are used in primary care and the most frequent reasons for antibiotic prescribing are acute upper and lower respiratory tract infections (ARTI)[5-7], although primarily of viral origin, and urinary tract infections[8]. Outpatient antibiotic use in Switzerland is relatively low compared to other European countries, but there is considerable variation in

prescription rates between Swiss regions with a relatively high use of macrolides and fluoroquinolones, a known risk factor for antibiotic resistance, in particular for *S. pneumoniae*[9]. To lower antibiotic prescriptions new strategies must be implemented that involve the '*4 P main stakeholders'*, prescribers, patients, payers and public health epidemiologists. Multiple approaches of stewardship programs to lower antibiotic use in primary care have been investigated using observational designs, typically before/after studies, or randomized trials. Interventions include provider or patient information tools, provision of treatment guidelines, communication training, delayed prescriptions and point of care testing.
A recent Health Technology Assessment from the United States found only low to moderate quality evidence on the effectiveness of these interventions due to insufficient study designs and inconsistent intervention effects[10]. Most studies selected a relatively small number of practices with motivated practitioners, and were too short to assess long-term effects on antibiotic prescription rates. Only few studies reported whether reduction in antibiotic prescriptions was safe and not associated with negative impact on patient relevant outcomes. Long term consequences of the interventions were insufficiently addressed and no study addressed the consequences of the intervention on antibiotic resistance. Trials on face-to-face provider education and academic detailing showed a more consistent reduction in overall antibiotic prescribing of 4% and about 3% per year and 1000 registered patients[11,12]. These interventions, however, are resource intense and therefore most likely not sustainable when applied at a large scale.

The investigated intervention is a nationwide intervention within the framework of the Swiss National Science Foundation program 72 on 'Antimicrobial Resistance' combining routine prescription and antibiotic resistance feedback in addition to the provision of evidence-based physician and patient education material.

We have conducted a *systematic review* to identify all randomized controlled trials (RCTs) investigating the effectiveness of routine monitoring and prescription feedback to lower antibiotic prescriptions in primary care. We searched for RCTs, including cluster RCTs, evaluating antibiotic prescription feedback interventions in primary care which are implementable on a system level, i.e. not involving direct physician contact, and without combined patient directed interventions. We searched PubMed from inception to 2016 for systematic reviews on antibiotic prescription feedback interventions. The two most recent relevant reviews were perused for eligible RCTs. For the time-period not covered by these reviews, we directly queried PubMed for RCTs (i.e. from 1 January 2012 to 14 April 2016). We combined MeSH headings and text terms for "antibiotics" and "feedback" and used the PubMed standard filter for systematic reviews and a Cochrane standard filter for RCTs.
There are three large-scale trials evaluating feedback interventions. One found no impact on antibiotic prescriptions when two mailed feedbacks, that addressed antibiotic prescribing and prescribing of four other drug groups, were given in 1995 to unselected Australian general practitioners[13]. The second found that a single feedback letter sent to the top 20% antibiotic prescribing general practitioners in 2014 in England reduced antibiotic prescribing by 3.3% over 6 months[14].

The third and largest trial in this field has recently been completed by our group[15]. We have conducted a nationwide pragmatic trial on quarterly personalized prescription feedback to reduce antibiotic overuse in primary care (ClinicalTrials.gov identifier: NCT01773824). We randomized the 2900 primary care physicians in Switzerland with the highest antibiotics prescription rates (median of 100.6 defined daily doses antibiotics per 100 consultations in the

year before the study). Physicians in the intervention group received quarterly personalized prescription feedback by mail and were provided with secured web-based access to analyses of their individual prescription data. We used routinely collected administrative claims data of SASIS/Santésuisse.
We found that the intervention may reduce prescriptions to older children and adolescents aged 6 to 18 years (-8·6% in the first year; 95%CI -14.8% to -1.9%) and younger adults (-4.6%; -7.9% to -1.2% in the second year). but not in the population at large (first year 0.8%; 2.6% to 4.3%; second year 1.7%; -5.1% to 1.7%). In addition we noted no shift towards less use of broad spectrum antibiotics. Data collection for this trial ended December 31, 2015. These findings underline the feasibility of such feedback, but we need a better understanding of the effects on patient-relevant outcomes, on antibiotic resistance, and of the underlying mechanisms leading to different effects in certain subgroups of patients before routine implementation in the Swiss health care system.

Objectives

Overall Objective: To evaluate a nationwide intervention program combining routine prescription and resistance feedback with the provision of evidence-based physician and patient education material within a large-scale pragmatic randomized controlled trial in primary care physicians in Switzerland.
Primary Objective: To evaluate whether this program reduces the total amount of antibiotics prescribed over a longer period, i.e. after 13 to 24 months (longer term intervention effect, second year of the study).
Secondary Objectives: To specifically explore the impact of this program on specific patient-populations defined by age groups, on prescribing of specific types of antibiotics, on patient relevant outcomes (i.e. hospitalizations), and costs.

Data-linkage substudy - Objective
To assess the association of antibiotic resistance and antibiotic use on patients with urinary tract infections (UTI) using linked data. Data linkage will be done between routinely collected claims data and the ANRESIS database.

Design and Outcomes

This is a pragmatic randomized, superiority, parallel group design trial with 1:1 randomization ratio in 3426 primary care physicians in Switzerland with high antibiotic prescription rates (i.e. among top 75% antibiotic prescribers). The trial is entirely based on routinely collected individual reimbursement claims data of the three largest Swiss health insurers using anonymized identifiers of physicians and patients and on routinely collected surveillance data on antibiotic resistance. Unit of analysis and randomization is the physician.

Primary outcome:
Overall antibiotic use, defined as prescribed antibiotics (based on packaged prescriptions derived from ATC codes) per 100 patient consultations (total patient population) evaluated over a period of 12 months, from month 13 to month 24 post randomization (longer term intervention effect).

Secondary outcomes:

(1) Overall antibiotic use defined as prescribed antibiotics per 100 patient consultations evaluated over a period of 12 months, from month 1 to 12 post randomization (short-term intervention effect);
(2) Overall antibiotic use defined as prescribed antibiotics per 100 patient consultations evaluated over a period of 24 months, from month 1 to month 24 post randomization, with two repeated measurements, over the first and the second 12 month period post randomization;
(3) Use of broad spectrum antibiotics in the total patient population (per 100 consultations)
   a. quinolones
   b. oral cephalosporines ;
(4) Hospitalizations rates
   a. all-cause
   b. related to infections (DRG-based definition)
(5) Antibiotic use (per 100 consultations) in four specific age groups, in patients
   a. <6 years
   b. 6 to <18 years
   c. 18 to <65 years
   d. ≥ 65 years
(6) Secondary outcomes (3) to (5) will be evaluated over two 12 month periods (from month 1 to month 12, and from month 13 to month 24).

Data-linkage substudy – Design and outcomes
We will use the privacy-preserving probability record linkage (P3RL) methodology to link the data-sets[16]. The linkage substudy will be limited to urinary tract infections and antibiotic resistance to amoxicillin-clavulanic acid, fosfomycin, nitrofurantoin trimethoprim-sulfamethoxazole, and fluoroquinolones.
Primary outcome:
(7) To explore any association of antibiotic resistance in urine samples from patients with potential risk factors. This analysis will allow us to evaluate for the first time the assessment of risk factors that may affect antibiotic resistance in urinary tract infections on the patient level in a nationwide population study.
Secondary outcome:
(8) To evaluate exploratively whether a reduction of antibiotic use observed in the nationwide intervention trial is associated with a reduction in antibiotic resistance in this subpopulation (e.g., lower rates of antibiotic resistance for the large-spectrum antibiotics across all patients with samples in the intervention group versus the control group over the first and second year of the study).

Origin of the data/material

We plan to use the same data for this study that is routinely used for reimbursement of medical treatments and services by the three largest Swiss health insurers Helsana, CSS, and Sanitas. There is no data specifically collected for the purpose of this study.
All data used by and provided to the investigators that are related to physicians or patients are encrypted using anonymized identifiers by the data managers of the collaborating insurers.

Data-linkage substudy:
ANRESIS is a national antimicrobial resistance surveillance system collecting data from 30 laboratories in Switzerland. Similar to the claims data, all data related to physicians or patients will be encrypted by the data manager of ANRESIS. The privacy-preserving probability record linkage (P3RL) process requires the anonymization of specific matching variables (e.g., ZSR numbers, date of sampling, etc.), those matching variable will also be encrypted. Hence, no

data will be made available to the investigators that might allow identifying an individual physician or patient.

Inclusion criteria

We plan to include and use data from

- Primary care physicians in Switzerland board certified with FMH title in general internal medicine or paediatrics & adolescent medicine who are
- above the 25th percentile of antibiotic prescribing and are
- consulting with at least 100 patients per year and who have a
- individual Zahlstellenregister (ZSR) number.

Exclusion criteria

There are no exclusion criteria.

For what personal health data / biological material is the authorization released for?

Physician prescription data originating from the insurance company databases will be analyzed, together with the corresponding data from the respective patient. The patient data will be anonymized directly from the insurance company, so that it will not be possible for the researchers to ascertain the identity of these patients nor of the physicians, but only to know the patient-physician linkage for those physician included in the intervention arm.
We would need basic information – using anonymous/encrypted patient-identifiers on:

- prescribing physician (canton, if pediatrician or general practitioner, if possibly working in a group office, “Gruppenpraxis”)
- consulted patient (canton, age-group in 5 years, if adult or children (below 18 years), gender, health insurer) with basic tarmed and “Analyse-Liste” positions (consultation date, which respiratory-tract or urinary-tract related diagnostic procedures or examinations were conducted), pharmacy-cost-group, prescription of antibiotics to this patients (date, amount, and ATC-code) and hospitalization information (if hospitalized and the date, duration, and type of infection-related DRG-code).

Data-linkage substudy:
In addition to the information listed above, antibiotic resistance to amoxicillin-clavulanic acid, fosfomycin, nitrofurantoin, trimethoprim-sulfamethoxazole, and fluoroquinolones from urine samples will be released to the investigators.

Motivation for the submission of informed consent waiver by the Ethics Committee

The intervention we aim to explore is similar to information campaigns in other countries where routinely prescribing feedback is given outside of a research setting, also based entirely on routine data from insurers. Guidelines and information material for patients are also routinely provided to general practitioners outside of research settings without any consideration of any theoretical risks. Such programs are commonly implemented without any ethical concerns.

We would like to scientifically evaluate the value of implementing such a program under real-life conditions with support of national physician associations and the national science foundation in the framework of a nationwide campaign to address the substantial public health threat of antibiotic resistance.
Since the physician intervention relies on a behavioral and information component it is not feasible to inform all physicians of the details of the study (i.e. they are able to opt out, but are not aware specifically that their antibiotic prescription behavior will be assessed). If we asked them for informed consent, we would not be able to determine whether the feedback is effective, as the physicians could change the behavior by knowing that we would be observing them. This would make it impossible to understand the real value of such an antibiotic stewardship program.
Regarding the patients, it would be highly unfeasible to identify, contact and inform all of the patients in entire Switzerland seen by these more than 3426 physicians, also because they are not aware of the study details and this may again considerably change and affect the intervention and destroy the concept of a “real world control group”.
These arguments also apply for the Data-linkage substudy.
This study will allow determining if prescription guidelines and feedback on antibiotic therapy are effective in reducing the rates of antibiotic resistance, which will benefit the entire Swiss population.

Confirmation that there will be no documented refusal

The project-leader confirms that no health-related individual data and no biological data will be used if there is a written or documented oral refusal by the respective person.

Any physician in the intervention group, upon receipt of their guideline and feedback package, has at any time-point the ability to anonymously opt out and to decline receiving any further information material. We will stop sending the information and not contact this person in any way so that this remains the usual care setting. We will analyze the anonymous routinely collected data for the purpose of conducting an intention-to-treat analysis to ensure internal validity of the trial.

Which individuals are allowed to transmit biological material and personal health data?

There will be no personal data that is not anonymized in this trial. All data provided by health insurers or ANRESIS will be anonymized to ensure confidentiality of records that could identify individual physicians and their patients, or laboratories.

Who is responsible for receiving the data / material in question?

No personal data that is not anonymized will be used in this trial by the investigators, all data provided by health insurers or ANRESIS will be anonymized.

Who, in the context of this research project, will be authorized to access personal health data and / or biological material?

Please see section above, this trial will not involve any data that is not anonymized after being processed by the health insurers or ANRESIS.

Who is responsible for the protection of the communicated data?

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Scientific Methodology

The statistical hypothesis to test is H_0: $\mu_1 = \mu_0$ versus H_1: $\mu_1 \neq \mu_0$
Where μ_1 is the population mean of the reduction (change score) in prescribed antibiotics per 100 patient consultations in the intervention arm and μ_0 is the population mean of the reduction in the control arm (primary outcome).
The null hypothesis H_0 will be tested against the alternative H_1 using ANCOVA.
In 2016, the baseline year, the inclusion criteria were fulfilled by 3646 physicians. The standard deviation of the prescription rate in the target population can be evaluated based on the data from the baseline year (2016), which is 0.059 on the raw scale and 0.438 on the log scale.

Power analysis based on bootstrapping:
Because another trial with the same target population was planned by CEB and to avoid any potential interference with the present trial (Benchmark II), 220 physicians were excluded from the eligible pool of physicians around the Basel region (BS, BL, AG, SO). Therefore, 3426 physicians remain to be randomized, i.e. 1713 physicians per arm in a 1:1 randomization ratio. The power analysis is based on a trial simulation from 50 bootstrap samples extracted from the pool of physicians to randomize. For each bootstrap sample we simulate a trial where we apply the effect we expect to observe in the treatment arm, also accounting for a 15% failure to respond, and for each sample we then test the difference by means of a Mann Whitney U test (Wilcoxon rank sum). Hence we evaluate the power for each bootstrap sample, and derive median and confidence intervals from the empirical distribution, which gives as an estimated power of: median: 0.93, 95% CI: 0.90 to 0.96.

Data-linkage substudy:
The direct association between bacterial resistance and antibiotic use will be assessed with a multilevel mixed logistic regression model adjusting for clustering by physicians. Further descriptive analyses will be performed to show associations between the antibiotic prescription rates of the GPs and the emergence of bacterial resistance. The analyses will also explore regional or patient age-group specific differences and whether a potential intervention effect of the intervention trial on antibiotic prescribing rate also impacted the emergence of bacterial resistance.

Obligation of notification

A change in the methods of the project, as well as the changes to the indications mentioned in the authorization, must be notified in advance to the competent ethics committee.

The conclusion or termination of the research project must be notified to the Ethics Committee within 90 days.

After completion of the study, a summary of the results will be sent to all included general participants.

Protection of data: encryption and preservation

All data provided by health insurers and ANRESIS will be anonymized to ensure the confidentiality of records that could identify individual physicians and their patients. The coordinating data manager from Sanitas will use the ZSR numbers (which are centrally distributed and provided for all physicians with licenses in Switzerland by SASIS/Santésuisse) to generate unique anonymous identifiers for all included physicians.
A unique patient identifier will be used by the health insurers for the analysis of anonymized claims data per physician, but this identifier will not be released to the study investigators or the study staff at any time. This trial will not involve or directly collect any prospective data from individual patients. The set-up for data collection and the appropriate anonymization of data is of outmost importance to comply with data protection rules.
All randomized study participants will be marked with an anonymous identifier. An encrypted list of all identifiers will be generated by each insurer and kept secure on a dedicated network directory for at least 10 years. The encryption will be done via AES-256 symmetric encryption of archive files. Respective passwords will be kept separate from the data.

The study investigators must not know which data comes from which insurer. To ensure that the insurers are not identifiable, an independent data center which is not part of the study group and not part of the insurers will act as intermediate data operator and receive the insurance data and provide them to the investigators without any variable or marker allowing to identify the insurer. The Clinical Trial Unit University Hospital Basel will act in this function, applying all established rules of data protection and anonymization.

The specified study datasets will be securely transferred in encrypted format from health insurers to the intermediate data operator who will then (after anonymizing the insurers) transfer the data to the study center at Basel Institute for Clinical Epidemiology & Biostatistics (CEB), University Hospital Basel.

Data-linkage substudy:

The privacy-preserving probability record linkage (P3RL) process requires an additional step to generate a link table. In the linkage process, data managers from the health insurances and ANRESIS will provide the encrypted matching variables (ZSR number, date of sampling, or date of sample arrival in the laboratory with ordered urine cultures). The linkage will be done using this information, and the link table will then be sent to the investigators of CEB, which allows identifying matched entries in the databases from the health insurers and ANRESIS.

Procedure in case of unencrypted / non-anonymous data

Not applicable, as no un-encrypted/non-anonymous personal data will be used in this trial.

Data storage information

The specified study datasets will be securely transferred in encrypted format from health insurers and ANRESIS to the intermediate data operator who will then (after anonymizing the insurers) transfer the data to the study center at Basel Institute for Clinical Epidemiology & Biostatistics (CEB), University Hospital Basel. All study data will be stored and processed on infrastructure located within the University Hospital Basel and the University of Basel. Data management will be conducted in accordance with the procedures used for trial data management by the clinical trial unit. Data processing and analysis will be done using the sciCORE infrastructure from the University of Basel. Access to the dataset will be strictly limited to the data manager and the biostatistician of the project.
All data may only be used for the study purpose. A contract between the principle investigator, health insurers and ANRESIS will be set-up to regulate all issues of data protection and data rights. All staff of CEB involved in the trial and the director of the Institute will sign a confidentially form.
Postal-addresses of physicians are included in records of the health insurers. Postal anonymized feedback forms will be generated through an automated process by CEB and packing of the envelopes will be centrally executed, maintaining anonymity of randomized physicians.
The password protected webpage for the trial for intervention support material and guidelines will be hosted by nine.ch, a dedicated hosting company in Zurich. A virtual server and separate off-site backup will be rented for the study duration, allowing expansion of storage and computing capacity in case of need (https://www.nine.ch/de/root/vserver/). The trial website and respective database, server and backup systems will be managed by Saccilotto Consulting, Basel

Duration of data storage

All study data will be archived for a minimum of 10 years after study termination or premature termination of the pragmatic trial.

Ethical and regulatory requirements

This project meets the regulatory requirements of LRUm and ORU and has been approved by the Ethics Committee.

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