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# A study protocol for a multicentre, cluster-randomised, superiority trial evaluating the impact of computerized decision support, audit and feedback on antibiotic use: The Computerized Antibiotic Stewardship Study (COMPASS)



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# A study protocol for a multicentre, cluster-randomised, superiority trial evaluating the impact of computerized decision support, audit and feedback on antibiotic use: The Computerized Antibiotic Stewardship Study (COMPASS)

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# ABSTRACT

**INTRODUCTION:** Inappropriate use of antimicrobials in hospitals contributes to antimicrobial resistance. Antimicrobial stewardship (AMS) interventions aim to improve antimicrobial prescribing, but they are often resource and personnel intensive. Computerized Decision Support Systems (CDSS) seem a promising tool to improve antimicrobial prescribing but have been insufficiently studied in clinical trials.

**METHODS AND ANALYSIS:** The COMPuterized Antibiotic Stewardship Study (COMPASS) trial is a publically funded, open-label, cluster-randomised, controlled superiority trial which aims to determine whether a multi-modal CDSS intervention integrated in the electronic health record (EHR) reduces overall antibiotic exposure in adult patients hospitalized in wards of two secondary and one tertiary care centre in Switzerland compared to "standard-of-care" AMS. Twenty-four hospital wards will be randomised 1:1 to either intervention or control, using a "pair-matching" approach based on baseline antibiotic use, specialty and centre. The intervention will consist of (1) decision support for the choice of antimicrobial treatment and duration of treatment for selected indications (based on indication entry), (2) accountable justification for deviation from the local guidelines (with regard to the choice of molecules and duration), (3) alerts for self-guided re-evaluation of treatment on calendar day 4 of antimicrobial therapy and (4) monthly ward-level feedback of antimicrobial prescribing indicators. The primary outcome will be the difference in overall systemic antibiotic use measured in days of therapy (DOT) per admission based on administration data recorded in the EHR over the whole intervention period (12 months), taking into account clustering. Secondary outcomes include qualitative and quantitative antimicrobial use indicators, economic outcomes and clinical, microbiological and patient safety indicators.

**ETHICS AND DISSEMINATION:** Ethics approval was obtained for all participating sites (CCER 2017-00454). The results of the trial will be submitted for publication in a peer-reviewed journal. Further dissemination activities will be presentations / posters at national and international conferences.

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# ARTICLE SUMMARY

**Strengths and limitations of this study**

- The use of a multicentre randomised design in a research area where there is a clear lack of high-quality trials (impact: increased internal validity)
- The intervention will be tested in a diverse setting of hospitals in different cultural / language regions of the same country (impact: increased external validity) and it is relatively easy to implement uniformly (impact: increased external validity)
- Overall, antimicrobial prescribing levels in the participating centres are already relatively low compared to levels in other countries (about 50-60 Defined Daily Dose (DDD) per 100 patient-days) (impact: reduced external validity; higher risk of "negative" trial)
- While the intervention should be implementable elsewhere, it requires modifications in the EHR / CPOE system which may be difficult to implement in settings using software by commercial vendors (impact: reduced external validity)
- This is a cluster randomised trial with the ward as the "unit of randomisation". A certain degree of "contamination" is therefore unavoidable, *e.g.* through physicians changing between wards, although the degree is lower than for an individual randomised trial (impact: higher risk of "negative" trial)

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# INTRODUCTION

Inappropriate use of antimicrobials in hospitals is one of the key drivers of antimicrobial resistance (AMR) and *Clostridium difficile* infection (CDI). The purpose of antimicrobial stewardship (AMS) is, by definition, to protect this limited resource and stave off the negative consequences of its inadequate use while at the same time optimizing patient outcomes.[1] AMS programs have been implemented in thousands of hospitals around the world, in some areas by legal mandate.[2, 3] While there is increasing evidence that AMS can generally reduce drug costs, AMR and CDI in the hospital setting, we still do not know which particular AMS interventions provide the best and most sustainable improvements in antibiotic prescribing with the best cost-effectiveness.[4-6] In particular, many AMS interventions are labor-intensive and require "manual" assessment of individual situations by dedicated experts such as infectious diseases specialists or pharmacists.[7-11] This is problematic since it limits interventions to a small proportion of all prescriptions. Moreover, it threatens sustainability, since there are always competing hospital priorities resulting in limited resources for AMS programs

There is thus a need to at least partially automate AMS interventions. The 2016 AMS guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America indicate moderate-quality evidence for the incorporation of CDSS at the time of prescribing.[12] Computerized decision support systems (CDSS) to improve antimicrobial use have been implemented before, but there is clearly a lack of high-quality studies assessing their impact on actual antimicrobial prescribing and patient outcomes. The vast majority of studies in this area are uncontrolled before-after studies which have a much higher risk of bias and lower external validity.[13] A recent systematic review of computerised decision support for antibiotic use in hospitals identified only six randomised controlled studies among the 81 studies included in the review, of which half (3) were single-site studies. [14] Another earlier systematic review, also mostly identified low-quality, single centre, before-after studies and concluded that "high quality, systematic, multi-site, comparative studies are critically needed to assist organizations in making informed decisions about the most effective IT interventions."[15] Furthermore, existing studies often limited assessment to specific situations and settings, such as increasing guideline compliance in the treatment of UTI[16] and critically ill patients[17] , and to

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improve empirical antibiotic treatment for patients with suspected bacterial infections.[18] CDSS are also often overly complex, poorly designed, not integrated into the workflow, expensive, or difficult to implement in heterogeneous clinical settings.[19]

The COMPASS trial aims to address this evidence-gap by assessing through a randomised multicenter trial, if a CDSS integrated into the workflow can reduce DOT per admission in the intervention wards compared to controlled wards, over a one-year period.

# METHODS AND ANALYSIS

## Study setting

COMPASS will be conducted in adult acute-care wards of three Swiss hospitals, one academic medical centre and two regional hospitals. HUG (Geneva University Hospitals) is one of the largest hospitals in Switzerland with about 1'800 beds and 700'000 patient-days per year.[20] HUG has deployed an in-house electronic health record (EHR) since 2000 and a computerized physician order entry system (CPOE) system since 2006.[21] ORL (Regional Hospital Lugano) and OSG (Regional Hospital Bellinzona) are the largest hospitals of Southern Switzerland, with respectively 306 and 228 beds, and about 100'000 and 72'000 patients-days per year. Both hospitals have developed and adapted an EHR and CPOE system based on the in-house system of HUG since 2008 and 2014, respectively. All three hospitals have AMS programs with regularly updated antimicrobial prescribing guidelines, review of all positive blood cultures, regular teaching sessions for physicians, and internal and external benchmarking of antibiotic use and resistance. Dedicated ward rounds in some divisions (*e.g.* the intensive care unit and hematologic or solid organ transplant wards), are also part of the AMS program at HUG; however, these units will not be included into COMPASS. The overall framework for the COMPASS intervention is identical in all study sites; given the particularities of each setting (different EHRs, different categories of hospitals; different language; different prescribing guidelines) some details of the intervention may slightly vary between sites.

## Intervention

The intervention will consist of four components (figure 1):

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(1) Decision support for antimicrobial treatment with regard to the choice of antimicrobial drugs based on indication entry and current, local guidelines with accountable justification for guideline deviation;

(2) Alerts for self-guided re-evaluation of antimicrobial therapy on calendar day 4 of therapy;

(3) Decision support for the duration of antimicrobial treatment based on indication entry and current, local guidelines with accountable justification for guideline deviation and;

(4) Regular feedback of unit-wide antimicrobial prescribing indicators

## (1) Decision support for antimicrobial treatment

When physicians prescribe a systemic antimicrobial agent (including antifungals & antivirals except antiretroviral drugs used for the treatment of HIV) in the CPOE they will be asked to select whether the treatment is used for empiric treatment, targeted treatment or prophylaxis and to select the main indication of treatment based on a pre-specified list of indications linked to an international terminology such as International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) and Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT). If a treatment recommendation exists in the local guidelines for the given indication and the treatment regimen prescribed deviates from this recommendation, the prescriber will be offered the choice to switch to the guideline-recommended treatment; otherwise prescribers will be asked to provide an “accountable justification” for the deviation from the guidelines (a predefined list of potential reasons will be provided with the availability to also enter free text). The proposed system ensures that each antibiotic prescription is linked to a retrievable indication, making it possible to assess prescribing quality and to provide specific decision support.

## (2) Self-guided evaluation alert

On the fourth calendar day of antimicrobial treatment, a visual electronic alert displayed in the patient’s electronic medical chart will remind prescribers to reassess treatment with regard to intravenous-oral switch, de-escalation or stopping therapy. The alert will not be blocking (i.e. if the alert is ignored by the prescriber the antimicrobial prescription will

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remain active), it will, however, continue to be displayed until it is addressed. Furthermore, the alert will also be displayed on the "visual synopsis" of all patients hospitalized in the ward, making it possible for nursing staff to remind prescribers to address the alert.

The re-evaluation of treatment will be self-guided, i.e. there will be no decision-support guiding treatment adaptation based on patient-specific data such as vital signs, microbiologic results or use of other medications. General information useful for re-evaluation, such as iv-oral switch criteria, will be provided as info-buttons. If the antimicrobial treatment is continued or modified, prescribers will be asked to reassess the indication (since the indication may change over a course of antimicrobial treatment). If the antimicrobial treatment is modified on calendar day 3, re-evaluation will be assumed to have taken place and no alert will be displayed on day 4.

### (3) Decision support for duration of treatment

At the time of re-evaluation, the guideline-concordant duration will be automatically proposed. If this duration is exceeded, a justification will have to be provided.

### (4) Systematic audit and feedback

Quality indicators of antimicrobial prescribing such as concordance with local guidelines (in terms of duration of therapy and drug) will be automatically assessed based on the information collected during the prescribing process. All physicians on a given intervention ward will receive monthly e-mails outlining the performance of the ward compared to the other participating wards and compared to the guideline recommendation (if applicable). The results will be presented graphically.

## Duration of the intervention period

The intervention period will last 12 months. If the intervention proves to be successful based on analyses of the data, the system will also be implemented in the control wards and the effect will continue to be monitored in all wards to assess the sustainability of the intervention after the end of the research study.

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## Control

The control will consist of routine, "standard-of-care" antimicrobial stewardship as described above.

## Sample size

The sample size calculation is based on the primary outcome (DOT per admission) and has been performed taking into account the pair-matched and clustered design of the study according to the approach proposed by Hayes and Bennett.[22] Assuming 12 wards per arm, with an average size of 500 admissions, antibiotic use of 4.0 DOT/admission in the control group with a standard deviation of 1.0 (based on preliminary antibiotic use data) and a two-sided type I error of 0.05 we would have a power of 80% to detect a relative difference in average DOT/admission between the intervention and control arm of at least 7.7%. Antibiotic stewardship interventions described in the published literature have often exceeded this effect size.[23]

## Inclusion criteria and randomisation

Twenty-four acute-wards fulfilling the inclusion criteria (table 1) will be recruited by approaching the heads of the concerned departments (16 wards at HUG, 4 wards at ORL and OSG each). Acute wards will be paired according to centre, specialty (e.g., medicine, surgery, geriatrics), and baseline antibiotic use in days of therapy (DOT)/admission. Wards will be randomised 1:1 to the intervention or control arm within each pair using an online random sequence generator (figure 2). The randomisation plan will be established by personnel not directly involved in the study. Depending on the recruitment of wards, specialities may be matched across ORL and OSG since due to the smaller size these hospitals may only have one ward per specialty (e.g. visceral surgery, orthopaedics). In that case randomisation may be constrained to make sure that each hospital has at least one intervention ward in either specialty (e.g. orthopaedics or visceral surgery).

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## Outcomes

Table 2 gives a detailed overview of the primary and secondary outcomes, the underlying hypothesis and the justification for the choice of outcomes.

### Primary outcome

The difference in overall systemic antibiotic use measured in days of therapy (DOT) of systemic antibiotic use per admission based on electronically recorded drug administration data (for details see table 2).[24] One DOT represents a specific antibiotic administered to an individual patient on a calendar day independent of dose and route.

### Secondary outcomes

Secondary outcomes include quantitative and qualitative antimicrobial use indicators, clinical outcomes, microbiologic outcomes, economic outcomes and user satisfaction (see table 2 for more detailed definitions).[25, 26]

## Blinding

Neither the study staff implementing the intervention, nor the physicians targeted by the intervention, nor the patients receiving treatments will be blinded to an individual ward's assignment group since the nature of the intervention makes this impossible. Extraction of the primary and secondary outcome measures will be performed primarily by administrative staff not involved in the study. The data analysts will be blinded to the treatment allocation.

## Study schedule

The intervention is scheduled to begin mid-2018.

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### Analysis

Outcome variables will first be summarized across treatment and intervention groups and then explored using descriptive statistics, taking into account the matched design by sandwich variance estimators for confidence intervals. The DOT/admission at the individual level will be compared between the intervention groups using a random effects poisson model with two levels, taking into account clustering within hospitals and the matched pairs. The following confounders will be considered: sex, age, type of comorbidities and type of admission (internal medicine versus other), whereby all variables that result in a change of >5% in the coefficient for the intervention effect in bivariate regression will be added to the multivariate model, and the most parsimonious model will be selected through the conditional AIC. Collinearity will be checked through a correlation matrix, whereby the most relevant, clinical variable will be selected in case of R-square>0.8.

### Data collection and management

Most data will be retrieved from the hospital's data warehouses. De-identified data will be stored in password protected Microscoft Excel files on secured hospital servers. For the secondary outcome "qualitative assessment of antibiotic use" a eCRF will be created in an electronic data capture system such as REDCap (REDCap Consortium).

For analysis data will be imported into a statistical program, such as Stata (StataCorp, College Station, Texas) or "R" (R Foundation for Statistical Computing). Only investigators directly involved in the trial will have access to the data. The data will be stored on secure servers with backup systems for 10 years.

### Patient and Public Involvement

Patients and Public were not involved in the development of the research question, study design or any other part of this protocol.

## ETHICS AND DISSEMINATION

The trial has been approved by the competent ethics committees in Geneva and Ticino (CCER n° 2017-00454). A waiver of informed consent by prescribers and patients was

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granted under the condition to provide an information leaflet to patients in the participating wards. Several publications in peer-reviewed journals are planned from this trial: these will include the description of the development of the intervention, and main findings of the trial. Furthermore, the findings will be presented at national and international conferences.

## DISCUSSION

To our knowledge the COMPASS trial will be one of the first multicentre, cluster randomised controlled trials to assess whether a pragmatic CDSS integrated into the electronic health record can reduce overall antibiotic use in a diverse setting of hospitals. Our study has several strengths and limitations which are outlined in the article summary. COMPASS addresses many of the limitations of previous studies regarding the impact of CDSS on antimicrobial use in hospitals.[13] A limitation of COMPASS is the fact that the combination of different interventions will make it difficult to identify which component is the most effective; this can hopefully be addressed in further research. We believe that COMPASS is innovative in combining relatively new strategies for AMS, such as “accountable justification” with well-established strategies like audit and feed-back leveraging the potentials of the electronic health record.[27, 28] If effective, similar systems could be adapted in many hospitals given the relatively “simple” design of the CDSS intervention.

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## AUTHORS' CONTRIBUTIONS

BDH conceived the original idea for this study, which was further developed with all authors. BDH, EB, SH, LK and RM secured funding for the study. BDH and GC wrote the first draft of this manuscript. MdK provided input regarding the sample size calculations and statistical analysis. The manuscript was reviewed and edited by all authors: MdK, BWS, RV, SH, LK, LE, RM, EB.

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## COMPETING INTERESTS STATEMENT

All authors declare no competing interests.

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## Table 1. Inclusion and exclusion criteria

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Cluster level [wards]** | • Acute-care wards with at least 150 admissions/year<br>• Use of CPOE | • Emergency room(s)<br>• Outpatient clinics<br>• Overflow wards<br>• Absence of a "matchable" ward regarding specialty and baseline antibiotic use<br>• Hematopoietic stem cell transplant wards<br>• ICU |
| **Physician level** | • All physicians involved in antibiotic prescribing decisions in the participating wards | • None |
| **Patient level** | • All patients hospitalized in the participating wards | • None |

**CPOE:** computerized physician order entry

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## Table 2. Main study outcomes and corresponding hypotheses evaluated within the COMPASS trial

| | Outcome component | Relevant hypothesis<br><br>(If not otherwise stated the hypothesis refers to the expected effect of the intervention) | Rationale for outcome selection |
|---|---|---|---|
| **Primary outcome** | Days of therapy (DOT) of antibiotics[a] per admission | Reduction in antibiotic use through shortening of duration of treatment and reduction in combination therapies | DOT is an easily measurable objectively assessable outcome that is supported by expert consensus.[24] Admission was chosen as the denominator for the primary outcome rather than patient-days since reductions in antimicrobial treatment duration (reflected by a reduction in DOT) may induce a reduction of length of stay (LOS). This may have as consequence that DOT per patient-days changes little despite a reduction in antibiotic exposure since both the numerator and denominator are reduced. |
| **Secondary outcomes: quantitative antimicrobial use**[b] | DOT per 100 patient-days (PD)<br><br>Defined Daily Doses (DDD) per 100 PD and per admission<br><br>Antimicrobial days (AD)[c] per 100 PD and per admission<br><br>Days per treatment period overall and for specific indications[d] | Reduction in antimicrobial use through shortening of duration of treatment and reduction in combination therapies | Defined daily doses (DDD) are the most widely used metric for antimicrobial consumption and are therefore most suitable for comparisons with other settings. Antimicrobial days (AD) are a further metric that has been proposed to assess antibiotic use. Both patient-days and admissions have been proposed as denominators.[24, 29-32]<br><br>A treatment period is defined as antibiotic treatment not interrupted by more than one calendar day or discharge |
| **Secondary outcomes: clinical outcomes** | 30 day-mortality | The intervention is safe and does not result in an increase in mortality or | Clinical outcomes are included to demonstrate the safety of the intervention, the improvement of quality of care and the absence of unintended consequences. The clinical outcomes |

| | | | |
|---|---|---|---|
| | In hospital mortality | readmissions | are chosen based on their objectivity, the ease of obtaining the data and expert consensus. [29, 33] |
| | Unplanned hospital readmissions within 30 days after discharge | | |
| | Hospital length of stay | Similar length of stay or a reduction in the length of stay | |
| | Intensive or intermediate care unit admission from COMPASS wards | No increase in the number of intensive care unit or intermediate care unit admissions | |
| **Secondary outcomes: qualitative antimicrobial use** | Concordance of empirical antibiotic therapy with local guidelines (taking into account justified exceptions) with regard to the choice of molecules and duration of treatment<br><br>Switch to oral therapy when appropriate<br><br>De-escalation of antimicrobial therapy by calendar day 4 of treatment<br><br>Appropriate diagnostic | Improved quality of antimicrobial use | Improving the quality of antimicrobial use is one of the key goals of antimicrobial stewardship (AMS). Valid, reliable and universally accepted metrics for measuring appropriateness of antimicrobial use are difficult to define and labour-intensive to assess.[31] Qualitative antimicrobial use outcomes will be assessed through manual review of a random selection of charts (at least 50 charts per ward over the 12 months period) by infectious diseases specialists using pre-specified criteria for appropriateness. A sub-selection of charts (about 10% of the sample) will be reviewed independently by 2 reviewers (blinded to ward assignment) to determine inter-observer variability. |

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| | exams | | |
| **Secondary outcomes: microbiologic outcomes and healthcare associated infections** | Incidence of healthcare facility onset *Clostridium difficile* denominated per 10 000 PD and admission (attributed to unit)<br><br>Incident clinical cultures with multi-drug resistant organisms (MRSA, ESBL-E, CPE, VRE, multidrug resistant *P. aeruginosa*) denominated per 1000 PD and admission | Reduced incidence of healthcare facility onset *C. difficile* infection<br><br>Reduced incidence of multidrug-resistant organisms | Limiting *Clostridium difficile* infections (CDI) and the emergence and transmission of AMR is one of the key goals of AMS. There is expert consensus that the incidence of CDI and drug-resistant pathogens are key metrics to assess the impact of AMS.[24]<br><br>Since these outcomes are influenced by numerous other factors and would require a very large sample size, they are secondary outcomes and not primary outcomes in this study. |
| **Secondary outcomes physician satisfaction** | User satisfaction with the system | Users will be satisfied with the system | A major obstacle to the use of CDSS is the lack of buy-in from prescribers and unintended consequences such as "alert fatigue". |
| **Secondary outcomes: economic** | Costs of administered antimicrobials (overall and by class) per admission and per admission receiving antibiotics<br><br>Costs of the intervention<br><br>Total costs of hospitalisation | Decreased overall direct costs for antimicrobials | Reducing the cost of antimicrobial therapy is a goal secondary to that of improving quality of care and patient safety but is one of great interest to administrators.[34] All costs will be assessed from the perspective of the hospital. |
| **Other outcomes** | Number of infectious diseases consultations | No difference in the number of infectious diseases consultations between the groups | An unintended consequence of the intervention may be an increase in the requests for infectious diseases consultations which may impact antibiotic use and patient outcomes.[35] |

[a] The primary outcome will be DOT for antibiotics belonging to Anatomical Therapeutic Chemical (ATC) Classification System class J01 (anti-infectives for systemic use) plus oral metronidazole (P01AB01), oral vancomycin (A07AA09), rifampicin (J04AB02) and fidaxomicin (A07AA12).

[b] In addition to overall antibiotic use as defined above, outcomes for DOT and DDD will also be assessed for different antibiotic classes, for antifungals, for non-HIV antivirals and for selected specific antibiotics.

[c] The metric “Antimicrobial day” (AD) is equivalent to “Length of Therapy” (LOT)[36]

[d] To make a comparison possible between intervention and control wards the “diagnosis” will be based on administrative discharge data. The most common infections (Community acquired pneumonia, upper urinary tract infection etc.) will be analyzed.

CPE : carbapenemase-producing *Enterobacteriaceae*; ESBL-E : extended-spectrum beta-lactamase producing *Enterobacteriaceae*; MRSA : methicillin-resistant *Staphylococcus aureus*; VRE: vancomycin-resistant enterococci.

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## Figure 1: COMPASS interventions

Legend: (1) Decision support for antimicrobial treatment will be provided when physician prescribes systemic antimicrobial agent (including antifungals & antivirals except antiretroviral drugs used for the treatment of HIV) in the CPOE. (2) On the fourth calendar day of antimicrobial treatment, a visual electronic alert displayed in the patient's electronic medical chart will remind prescribers to reassess treatment with regard to intravenous-oral switch, de-escalation or stopping therapy. (3) At the time of re-evaluation, the guideline-concordant duration will be automatically proposed. If this duration is exceeded, a justification will have to be provided. (4) All physicians on a given intervention ward will receive monthly e-mails outlining the performance of the ward compared to the other participating wards and compared to the guideline recommendation.

## Figure 2: Randomisation scheme

Legend: Twenty-four acute-wards fulfilling the inclusion criteria will be recruited (16 wards at HUG, 4 wards at ORL and OSG each). Acute wards will be paired according to centre, specialty (e.g., medicine, surgery, geriatrics), and baseline antibiotic use in days of therapy (DOT)/admission. Wards will be randomised 1:1 to the intervention or control arm within each pair using an online random sequence generator.

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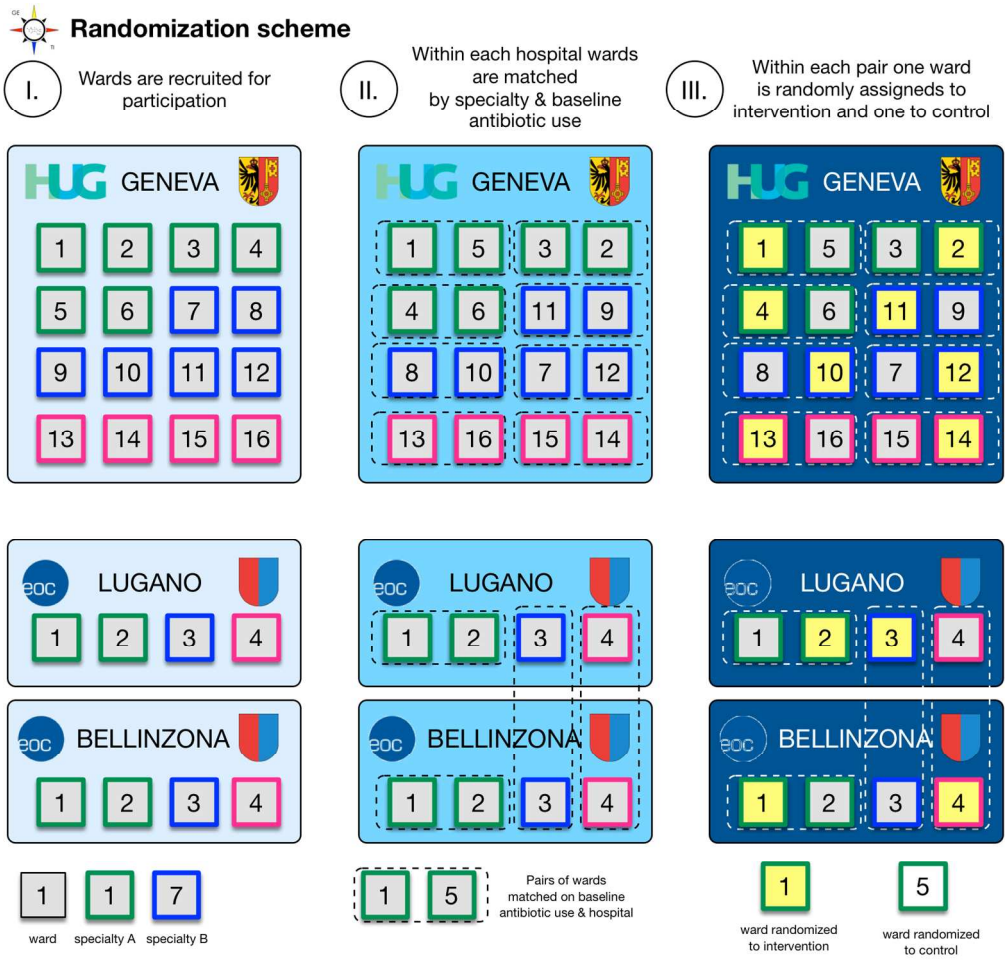


Figure 2: Randomisation scheme.
Legend:Twenty-four acute-wards fulfilling the inclusion criteria will be recruited (16 wards at HUG, 4 wards at ORL and OSG each). Acute wards will be paired according to centre, specialty (e.g., medicine, surgery, geriatrics), and baseline antibiotic use in days of therapy (DOT)/admission. Wards will be randomised 1:1 to the intervention or control arm within each pair using an online random sequence generator.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Reported on page /line No (NA: not applicable) |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | Page 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | Page 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | NA |
| Protocol version | 3 | Date and version identifier | |
| Funding | 4 | Sources and types of financial, material, and other support | Page 15/line 21-23 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | Page 1 |
| | 5b | Name and contact information for the trial sponsor | Page 1 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | Page 15 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | NA |
| **Introduction** | | | |

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| | | | |
|---|---|---|---|
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | Page 4 |
| | 6b | Explanation for choice of comparators | Page 8 |
| Objectives | 7 | Specific objectives or hypotheses | Pages 5, 9 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | Pages 5, 8, 9 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | Page 5 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | Page 8 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | Pages 5-7 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | NA |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | Page 7 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | Pages 5-6 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | Page 9, Table 2 |



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| | | | |
|---|---|---|---|
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Pages 7, 9 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | Page 8 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | Page 8 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | Page 8 and figure 2 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | Page 8 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | Page 8 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | Page 9 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | NA |
| **Methods: Data collection, management, and analysis** | | | |



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| | | | |
|---|---|---|---|
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | Page 10 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | NA |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | Page 10 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | Page 10 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | NA |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | NA |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | NA |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | NA |


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| | | | |
|---|---|---|---|
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | NA |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | NA |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | Pages 10-11 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | NA |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | Page 10 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | NA |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | Page 10 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | Page 15 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | Page 10 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | NA |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | Pages 10-11 |

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| | | | |
|---|---|---|---|
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | Page 15 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | NA |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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# A study protocol for a multicentre, cluster-randomised, superiority trial evaluating the impact of computerized decision support, audit and feedback on antibiotic use: The Computerized Antibiotic Stewardship Study (COMPASS)



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|---|---|
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| Primary Subject Heading: | Infectious diseases |
| Secondary Subject Heading: | Health informatics |
| Keywords: | antimicrobial stewardship, computerized decision support system, cluster-randomised trial |



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Figure_1 (34).jpg

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# A study protocol for a multicentre, cluster-randomised, superiority trial evaluating the impact of computerized decision support, audit and feedback on antibiotic use: The Computerized Antibiotic Stewardship Study (COMPASS)

## AUTHORS AND AFFILIATIONS

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# ABSTRACT

**INTRODUCTION:** Inappropriate use of antimicrobials in hospitals contributes to antimicrobial resistance. Antimicrobial stewardship (AMS) interventions aim to improve antimicrobial prescribing, but they are often resource and personnel intensive. Computerized Decision Support Systems (CDSS) seem a promising tool to improve antimicrobial prescribing but have been insufficiently studied in clinical trials.

**METHODS AND ANALYSIS:** The COMPuterized Antibiotic Stewardship Study (COMPASS) trial is a publically funded, open-label, cluster-randomised, controlled superiority trial which aims to determine whether a multi-modal CDSS intervention integrated in the electronic health record (EHR) reduces overall antibiotic exposure in adult patients hospitalized in wards of two secondary and one tertiary care centre in Switzerland compared to "standard-of-care" AMS. Twenty-four hospital wards will be randomised 1:1 to either intervention or control, using a "pair-matching" approach based on baseline antibiotic use, specialty and centre. The intervention will consist of (1) decision support for the choice of antimicrobial treatment and duration of treatment for selected indications (based on indication entry), (2) accountable justification for deviation from the local guidelines (with regard to the choice of molecules and duration), (3) alerts for self-guided re-evaluation of treatment on calendar day 4 of antimicrobial therapy and (4) monthly ward-level feedback of antimicrobial prescribing indicators. The primary outcome will be the difference in overall systemic antibiotic use measured in days of therapy (DOT) per admission based on administration data recorded in the EHR over the whole intervention period (12 months), taking into account clustering. Secondary outcomes include qualitative and quantitative antimicrobial use indicators, economic outcomes and clinical, microbiological and patient safety indicators.

**ETHICS AND DISSEMINATION:** Ethics approval was obtained for all participating sites (CCER 2017-00454). The results of the trial will be submitted for publication in a peer-reviewed journal. Further dissemination activities will be presentations / posters at national and international conferences.

**TRIAL REGISTRATION NUMBER:** NCT03120975


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# ARTICLE SUMMARY

**Strengths and limitations of this study**

- The use of a multicentre randomised design in a research area where there is a clear lack of high-quality trials (impact: increased internal validity)
- The intervention will be tested in a diverse setting of hospitals in different cultural / language regions of the same country (impact: increased external validity) and it is relatively easy to implement uniformly (impact: increased external validity)
- Overall, antimicrobial prescribing levels in the participating centres are already relatively low compared to levels in other countries (about 50-60 Defined Daily Dose (DDD) per 100 patient-days) (impact: reduced external validity; higher risk of "negative" trial)
- While the intervention should be implementable elsewhere, it requires modifications in the EHR / CPOE system which may be difficult to implement in settings using software by commercial vendors (impact: reduced external validity)
- This is a cluster randomised trial with the ward as the "unit of randomisation". A certain degree of "contamination" is therefore unavoidable, *e.g.* through physicians changing between wards, although the degree is lower than for an individual randomised trial (impact: higher risk of "negative" trial)

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# INTRODUCTION

Inappropriate use of antimicrobials in hospitals is one of the key drivers of antimicrobial resistance (AMR) and *Clostridium difficile* infection (CDI). The purpose of antimicrobial stewardship (AMS) is, by definition, to protect this limited resource and stave off the negative consequences of its inadequate use while at the same time optimizing patient outcomes.[1] AMS programs have been implemented in thousands of hospitals around the world, in some areas by legal mandate.[2, 3] While there is increasing evidence that AMS can generally reduce drug costs, AMR and CDI in the hospital setting, we still do not know which particular AMS interventions provide the best and most sustainable improvements in antibiotic prescribing with the best cost-effectiveness.[4-6] In particular, many AMS interventions are labor-intensive and require "manual" assessment of individual situations by dedicated experts such as infectious diseases specialists or pharmacists.[7-11] This is problematic since it limits interventions to a small proportion of all prescriptions. Moreover, it threatens sustainability, since there are always competing hospital priorities resulting in limited resources for AMS programs

There is thus a need to at least partially automate AMS interventions. The 2016 AMS guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America indicate moderate-quality evidence for the incorporation of CDSS at the time of prescribing.[12] Computerized decision support systems (CDSS) to improve antimicrobial use have been implemented before, but there is clearly a lack of high-quality studies assessing their impact on actual antimicrobial prescribing and patient outcomes. The vast majority of studies in this area are uncontrolled before-after studies which have a much higher risk of bias and lower external validity.[13] A recent systematic review of computerised decision support for antibiotic use in hospitals identified only six randomised controlled studies among the 81 studies included in the review, of which half (3) were single-site studies. [14] Another earlier systematic review, also mostly identified low-quality, single centre, before-after studies and concluded that "high quality, systematic, multi-site, comparative studies are critically needed to assist organizations in making informed decisions about the most effective IT interventions."[15] Furthermore, existing studies often limited assessment to specific situations and settings, such as increasing guideline compliance in the treatment of UTI[16] and critically ill patients[17] , and to

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improve empirical antibiotic treatment for patients with suspected bacterial infections.[18] CDSS are also often overly complex, poorly designed, not integrated into the workflow, expensive, or difficult to implement in heterogeneous clinical settings.[19]

The COMPASS trial aims to address this evidence-gap by assessing through a randomised multicenter trial, if a CDSS integrated into the workflow can reduce DOT per admission in the intervention wards compared to controlled wards, over a one-year period.

# METHODS AND ANALYSIS

## Study setting

COMPASS will be conducted in adult acute-care wards of three Swiss hospitals, one academic medical centre and two regional hospitals. HUG (Geneva University Hospitals) is one of the largest hospitals in Switzerland with about 1'800 beds and 700'000 patient-days per year.[20] HUG has deployed an in-house electronic health record (EHR) since 2000 and a computerized physician order entry system (CPOE) system since 2006.[21] ORL (Regional Hospital Lugano) and OSG (Regional Hospital Bellinzona) are the largest hospitals of Southern Switzerland, with respectively 306 and 228 beds, and about 100'000 and 72'000 patients-days per year. Both hospitals have developed and adapted an EHR and CPOE system based on the in-house system of HUG since 2008 and 2014, respectively. All three hospitals have AMS programs with regularly updated antimicrobial prescribing guidelines, review of all positive blood cultures, regular teaching sessions for physicians, and internal and external benchmarking of antibiotic use and resistance. Dedicated ward rounds in some divisions (*e.g.* the intensive care unit and hematologic or solid organ transplant wards), are also part of the AMS program at HUG; however, these units will not be included into COMPASS. The overall framework for the COMPASS intervention is identical in all study sites; given the particularities of each setting (different EHRs, different categories of hospitals; different language; different prescribing guidelines) some details of the intervention may slightly vary between sites.

## Intervention

The intervention will consist of four components (figure 1):

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(1) Decision support for antimicrobial treatment with regard to the choice of antimicrobial drugs based on indication entry and current, local guidelines with accountable justification for guideline deviation;

(2) Alerts for self-guided re-evaluation of antimicrobial therapy on calendar day 4 of therapy;

(3) Decision support for the duration of antimicrobial treatment based on indication entry and current, local guidelines with accountable justification for guideline deviation and;

(4) Regular feedback of unit-wide antimicrobial prescribing indicators

## (1) Decision support for antimicrobial treatment

When physicians prescribe a systemic antimicrobial agent (including antifungals & antivirals except antiretroviral drugs used for the treatment of HIV) in the CPOE they will be asked to select whether the treatment is used for empiric treatment, targeted treatment or prophylaxis and to select the main indication of treatment based on a pre-specified list of indications linked to an international terminology such as International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) and Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT). If a treatment recommendation exists in the local guidelines for the given indication and the treatment regimen prescribed deviates from this recommendation, the prescriber will be offered the choice to switch to the guideline-recommended treatment; otherwise prescribers will be asked to provide an “accountable justification” for the deviation from the guidelines (a predefined list of potential reasons will be provided with the availability to also enter free text). The proposed system ensures that each antibiotic prescription is linked to a retrievable indication, making it possible to assess prescribing quality and to provide specific decision support.

## (2) Self-guided evaluation alert

On the fourth calendar day of antimicrobial treatment, a visual electronic alert displayed in the patient’s electronic medical chart will remind prescribers to reassess treatment with regard to intravenous-oral switch, de-escalation or stopping therapy. The alert will not be blocking (i.e. if the alert is ignored by the prescriber the antimicrobial prescription will

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remain active), it will, however, continue to be displayed until it is addressed. Furthermore, the alert will also be displayed on the "visual synopsis" of all patients hospitalized in the ward, making it possible for nursing staff to remind prescribers to address the alert.

The re-evaluation of treatment will be self-guided, i.e. there will be no decision-support guiding treatment adaptation based on patient-specific data such as vital signs, microbiologic results or use of other medications. General information useful for re-evaluation, such as iv-oral switch criteria, will be provided as info-buttons. If the antimicrobial treatment is continued or modified, prescribers will be asked to reassess the indication (since the indication may change over a course of antimicrobial treatment). If the antimicrobial treatment is modified on calendar day 3, re-evaluation will be assumed to have taken place and no alert will be displayed on day 4.

### (3) Decision support for duration of treatment

At the time of re-evaluation, the guideline-concordant duration will be automatically proposed. If this duration is exceeded, a justification will have to be provided.

### (4) Systematic audit and feedback

Quality indicators of antimicrobial prescribing such as concordance with local guidelines (in terms of duration of therapy and drug) will be automatically assessed based on the information collected during the prescribing process. All physicians on a given intervention ward will receive monthly e-mails outlining the performance of the ward compared to the other participating wards and compared to the guideline recommendation (if applicable). The results will be presented graphically.

## Duration of the intervention period

The intervention period will last 12 months. If the intervention proves to be successful based on analyses of the data, the system will also be implemented in the control wards and the effect will continue to be monitored in all wards to assess the sustainability of the intervention after the end of the research study.

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## Control

The control will consist of routine, "standard-of-care" antimicrobial stewardship as described above.

## Sample size

The sample size calculation is based on the primary outcome (DOT per admission) and has been performed taking into account the pair-matched and clustered design of the study according to the approach proposed by Hayes and Bennett.[22] Assuming 12 wards per arm, with an average size of 500 admissions, antibiotic use of 4.0 DOT/admission in the control group with a standard deviation of 1.0 (based on preliminary antibiotic use data) and a two-sided type I error of 0.05 we would have a power of 80% to detect a relative difference in average DOT/admission between the intervention and control arm of at least 7.7%. Antibiotic stewardship interventions described in the published literature have often exceeded this effect size.[23]

## Inclusion criteria and randomisation

Twenty-four acute-wards fulfilling the inclusion criteria (table 1) will be recruited by approaching the heads of the concerned departments (16 wards at HUG, 4 wards at ORL and OSG each). Acute wards will be paired according to centre, specialty (e.g., medicine, surgery, geriatrics), and baseline antibiotic use in days of therapy (DOT)/admission. Wards will be randomised 1:1 to the intervention or control arm within each pair using an online random sequence generator (figure 2). The randomisation plan will be established by personnel not directly involved in the study. Depending on the recruitment of wards, specialities may be matched across ORL and OSG since due to the smaller size these hospitals may only have one ward per specialty (e.g. visceral surgery, orthopaedics). In that case randomisation may be constrained to make sure that each hospital has at least one intervention ward in either specialty (e.g. orthopaedics or visceral surgery).

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## Outcomes

Table 2 gives a detailed overview of the primary and secondary outcomes, the underlying hypothesis and the justification for the choice of outcomes.

### Primary outcome

The difference in overall systemic antibiotic use measured in days of therapy (DOT) of systemic antibiotic use per admission based on electronically recorded drug administration data (for details see table 2).[24] One DOT represents a specific antibiotic administered to an individual patient on a calendar day independent of dose and route.

### Secondary outcomes

Secondary outcomes include quantitative and qualitative antimicrobial use indicators, clinical outcomes, microbiologic outcomes, economic outcomes and user satisfaction (see table 2 for more detailed definitions).[25, 26]

## Blinding

Neither the study staff implementing the intervention, nor the physicians targeted by the intervention, nor the patients receiving treatments will be blinded to an individual ward's assignment group since the nature of the intervention makes this impossible. Extraction of the primary and secondary outcome measures will be performed primarily by administrative staff not involved in the study. The data analysts will be blinded to the treatment allocation.

## Study schedule

The intervention is scheduled to begin mid-2018.

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### Analysis

Outcome variables will first be summarized across treatment and intervention groups and then explored using descriptive statistics, taking into account the matched design by sandwich variance estimators for confidence intervals. The DOT/admission at the individual level will be compared between the intervention groups using a random effects poisson model with two levels, taking into account clustering within hospitals and the matched pairs. The following confounders will be considered: sex, age, type of comorbidities and type of admission (internal medicine versus other), whereby all variables that result in a change of >5% in the coefficient for the intervention effect in bivariate regression will be added to the multivariate model, and the most parsimonious model will be selected through the conditional AIC. Collinearity will be checked through a correlation matrix, whereby the most relevant, clinical variable will be selected in case of R-square>0.8.

### Data collection and management

Most data will be retrieved from the hospital's data warehouses. De-identified data will be stored in password protected Microscoft Excel files on secured hospital servers. For the secondary outcome "qualitative assessment of antibiotic use" a eCRF will be created in an electronic data capture system such as REDCap (REDCap Consortium).

For analysis data will be imported into a statistical program, such as Stata (StataCorp, College Station, Texas) or "R" (R Foundation for Statistical Computing). Only investigators directly involved in the trial will have access to the data. The data will be stored on secure servers with backup systems for 10 years.

### Patient and Public Involvement

Patients and Public were not involved in the development of the research question, study design or any other part of this protocol.

## ETHICS AND DISSEMINATION

The trial has been approved by the competent ethics committees in Geneva and Ticino (CCER n° 2017-00454). A waiver of informed consent by prescribers and patients was

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granted under the condition to provide an information leaflet to patients in the participating wards. Several publications in peer-reviewed journals are planned from this trial: these will include the description of the development of the intervention, and main findings of the trial. Furthermore, the findings will be presented at national and international conferences.

## DISCUSSION

To our knowledge the COMPASS trial will be one of the first multicentre, cluster randomised controlled trials to assess whether a pragmatic CDSS integrated into the electronic health record can reduce overall antibiotic use in a diverse setting of hospitals. Our study has several strengths and limitations which are outlined in the article summary. COMPASS addresses many of the limitations of previous studies regarding the impact of CDSS on antimicrobial use in hospitals.[13] A limitation of COMPASS is the fact that the combination of different interventions will make it difficult to identify which component is the most effective; this can hopefully be addressed in further research. We believe that COMPASS is innovative in combining relatively new strategies for AMS, such as “accountable justification” with well-established strategies like audit and feed-back leveraging the potentials of the electronic health record.[27, 28] If effective, similar systems could be adapted in many hospitals given the relatively “simple” design of the CDSS intervention.

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## AUTHORS' CONTRIBUTIONS

BDH conceived the original idea for this study, which was further developed with all authors. BDH, EB, SH, LK and RM secured funding for the study. BDH and GC wrote the first draft of this manuscript. MdK provided input regarding the sample size calculations and statistical analysis. The manuscript was reviewed and edited by all authors: MdK, BWS, RV, SH, LK, LE, RM, EB.

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## COMPETING INTERESTS STATEMENT

All authors declare no competing interests.

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## Table 1. Inclusion and exclusion criteria

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Cluster level [wards]** | • Acute-care wards with at least 150 admissions/year<br>• Use of CPOE | • Emergency room(s)<br>• Outpatient clinics<br>• Overflow wards<br>• Absence of a "matchable" ward regarding specialty and baseline antibiotic use<br>• Hematopoietic stem cell transplant wards<br>• ICU |
| **Physician level** | • All physicians involved in antibiotic prescribing decisions in the participating wards | • None |
| **Patient level** | • All patients hospitalized in the participating wards | • None |

**CPOE:** computerized physician order entry

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## Table 2. Main study outcomes and corresponding hypotheses evaluated within the COMPASS trial

| | Outcome component | Relevant hypothesis<br><br>(If not otherwise stated the hypothesis refers to the expected effect of the intervention) | Rationale for outcome selection |
|---|---|---|---|
| **Primary outcome** | Days of therapy (DOT) of antibiotics[a] per admission | Reduction in antibiotic use through shortening of duration of treatment and reduction in combination therapies | DOT is an easily measurable objectively assessable outcome that is supported by expert consensus.[24] Admission was chosen as the denominator for the primary outcome rather than patient-days since reductions in antimicrobial treatment duration (reflected by a reduction in DOT) may induce a reduction of length of stay (LOS). This may have as consequence that DOT per patient-days changes little despite a reduction in antibiotic exposure since both the numerator and denominator are reduced. |
| **Secondary outcomes: quantitative antimicrobial use**[b] | DOT per 100 patient-days (PD)<br><br>Defined Daily Doses (DDD) per 100 PD and per admission<br><br>Antimicrobial days (AD)[c] per 100 PD and per admission<br><br>Days per treatment period overall and for specific indications[d] | Reduction in antimicrobial use through shortening of duration of treatment and reduction in combination therapies | Defined daily doses (DDD) are the most widely used metric for antimicrobial consumption and are therefore most suitable for comparisons with other settings. Antimicrobial days (AD) are a further metric that has been proposed to assess antibiotic use. Both patient-days and admissions have been proposed as denominators.[24, 29-32]<br><br>A treatment period is defined as antibiotic treatment not interrupted by more than one calendar day or discharge |
| **Secondary outcomes: clinical outcomes** | 30 day-mortality | The intervention is safe and does not result in an increase in mortality or | Clinical outcomes are included to demonstrate the safety of the intervention, the improvement of quality of care and the absence of unintended consequences. The clinical outcomes |

| | | | |
|---|---|---|---|
| | In hospital mortality | readmissions | are chosen based on their objectivity, the ease of obtaining the data and expert consensus. [29, 33] |
| | Unplanned hospital readmissions within 30 days after discharge | | |
| | Hospital length of stay | Similar length of stay or a reduction in the length of stay | |
| | Intensive or intermediate care unit admission from COMPASS wards | No increase in the number of intensive care unit or intermediate care unit admissions | |
| **Secondary outcomes: qualitative antimicrobial use** | Concordance of empirical antibiotic therapy with local guidelines (taking into account justified exceptions) with regard to the choice of molecules and duration of treatment | Improved quality of antimicrobial use | Improving the quality of antimicrobial use is one of the key goals of antimicrobial stewardship (AMS). Valid, reliable and universally accepted metrics for measuring appropriateness of antimicrobial use are difficult to define and labour-intensive to assess.[31] Qualitative antimicrobial use outcomes will be assessed through manual review of a random selection of charts (at least 50 charts per ward over the 12 months period) by infectious diseases specialists using pre-specified criteria for appropriateness. A sub-selection of charts (about 10% of the sample) will be reviewed independently by 2 reviewers (blinded to ward assignment) to determine inter-observer variability. |
| | Switch to oral therapy when appropriate | | |
| | De-escalation of antimicrobial therapy by calendar day 4 of treatment | | |
| | Appropriate diagnostic | | |

| | | | |
|---|---|---|---|
| | exams | | |
| **Secondary outcomes: microbiologic outcomes and healthcare associated infections** | Incidence of healthcare facility onset *Clostridium difficile* denominated per 10 000 PD and admission (attributed to unit)<br><br>Incident clinical cultures with multi-drug resistant organisms (MRSA, ESBL-E, CPE, VRE, multidrug resistant *P. aeruginosa*) denominated per 1000 PD and admission | Reduced incidence of healthcare facility onset *C. difficile* infection<br><br>Reduced incidence of multidrug-resistant organisms | Limiting *Clostridium difficile* infections (CDI) and the emergence and transmission of AMR is one of the key goals of AMS. There is expert consensus that the incidence of CDI and drug-resistant pathogens are key metrics to assess the impact of AMS.[24]<br><br>Since these outcomes are influenced by numerous other factors and would require a very large sample size, they are secondary outcomes and not primary outcomes in this study. |
| **Secondary outcomes physician satisfaction** | User satisfaction with the system | Users will be satisfied with the system | A major obstacle to the use of CDSS is the lack of buy-in from prescribers and unintended consequences such as "alert fatigue". |
| **Secondary outcomes: economic** | Costs of administered antimicrobials (overall and by class) per admission and per admission receiving antibiotics<br><br>Costs of the intervention<br><br>Total costs of hospitalisation | Decreased overall direct costs for antimicrobials | Reducing the cost of antimicrobial therapy is a goal secondary to that of improving quality of care and patient safety but is one of great interest to administrators.[34] All costs will be assessed from the perspective of the hospital. |
| **Other outcomes** | Number of infectious diseases consultations | No difference in the number of infectious diseases consultations between the groups | An unintended consequence of the intervention may be an increase in the requests for infectious diseases consultations which may impact antibiotic use and patient outcomes.[35] |

[a] The primary outcome will be DOT for antibiotics belonging to Anatomical Therapeutic Chemical (ATC) Classification System class J01 (anti-infectives for systemic use) plus oral metronidazole (P01AB01), oral vancomycin (A07AA09), rifampicin (J04AB02) and fidaxomicin (A07AA12).

[b] In addition to overall antibiotic use as defined above, outcomes for DOT and DDD will also be assessed for different antibiotic classes, for antifungals, for non-HIV antivirals and for selected specific antibiotics.

[c] The metric “Antimicrobial day” (AD) is equivalent to “Length of Therapy” (LOT)[36]

[d] To make a comparison possible between intervention and control wards the “diagnosis” will be based on administrative discharge data. The most common infections (Community acquired pneumonia, upper urinary tract infection etc.) will be analyzed.

CPE : carbapenemase-producing *Enterobacteriaceae*; ESBL-E : extended-spectrum beta-lactamase producing *Enterobacteriaceae*; MRSA : methicillin-resistant *Staphylococcus aureus*; VRE: vancomycin-resistant enterococci.

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## Figure 1: COMPASS interventions

Legend: (1) Decision support for antimicrobial treatment will be provided when physician prescribes systemic antimicrobial agent (including antifungals & antivirals except antiretroviral drugs used for the treatment of HIV) in the CPOE. (2) On the fourth calendar day of antimicrobial treatment, a visual electronic alert displayed in the patient's electronic medical chart will remind prescribers to reassess treatment with regard to intravenous-oral switch, de-escalation or stopping therapy. (3) At the time of re-evaluation, the guideline-concordant duration will be automatically proposed. If this duration is exceeded, a justification will have to be provided. (4) All physicians on a given intervention ward will receive monthly e-mails outlining the performance of the ward compared to the other participating wards and compared to the guideline recommendation.

## Figure 2: Randomisation scheme

Legend: Twenty-four acute-wards fulfilling the inclusion criteria will be recruited (16 wards at HUG, 4 wards at ORL and OSG each). Acute wards will be paired according to centre, specialty (e.g., medicine, surgery, geriatrics), and baseline antibiotic use in days of therapy (DOT)/admission. Wards will be randomised 1:1 to the intervention or control arm within each pair using an online random sequence generator.

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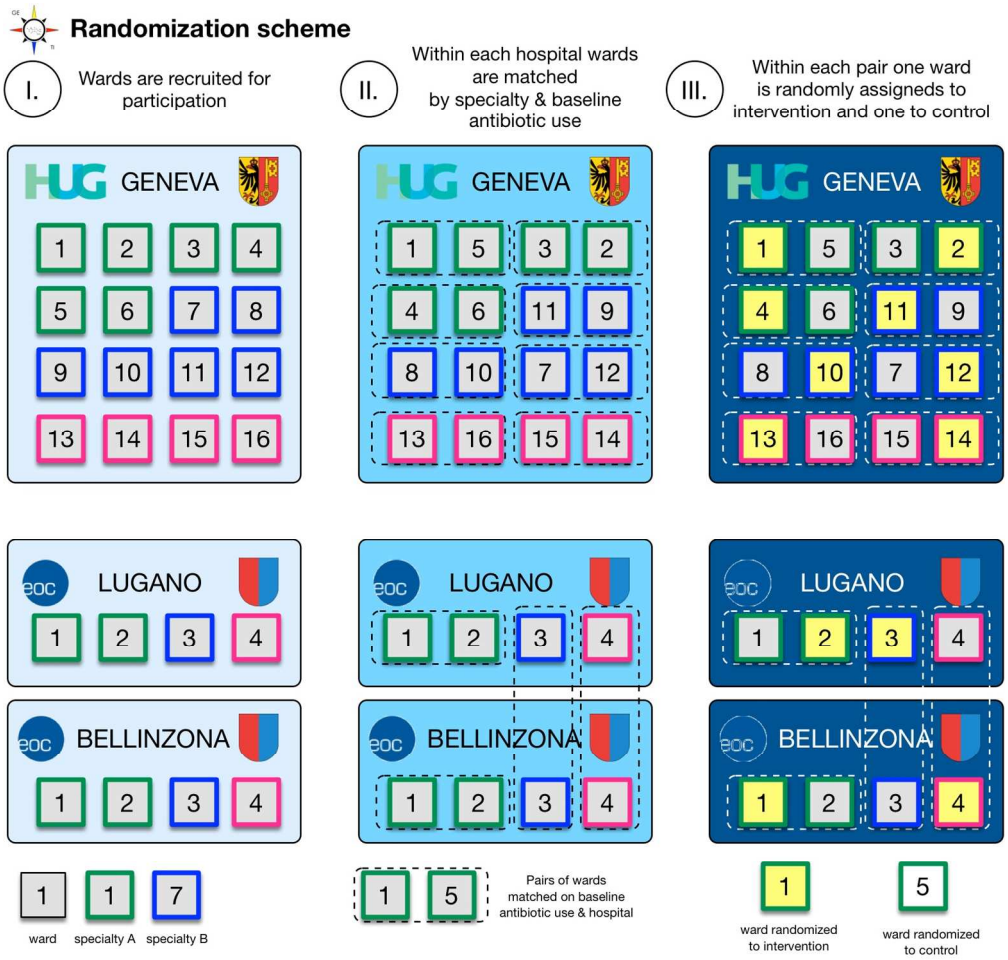
Randomization scheme
I.
Wards are recruited for participation
II.
Within each hospital wards are matched by specialty & baseline antibiotic use
III.
Within each pair one ward is randomly assigneds to intervention and one to control
HUG GENEVA
1 2 3 4
5 6 7 8
9 10 11 12
13 14 15 16
HUG GENEVA
1 5 3 2
4 6 11 9
8 10 7 12
13 16 15 14
HUG GENEVA
1 5 3 2
4 6 11 9
8 10 7 12
13 16 15 14
eoc LUGANO
1 2 3 4
eoc BELLINZONA
1 2 3 4
eoc LUGANO
1 2 3 4
eoc BELLINZONA
1 2 3 4
eoc LUGANO
1 2 3 4
eoc BELLINZONA
1 2 3 4
1 1 7
ward specialty A specialty B
1 5
Pairs of wards matched on baseline antibiotic use & hospital
1
ward randomized to intervention
5
ward randomized to control

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Reported on page /line No |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | Page 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | Page 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | Pages 11-12 |
| Protocol version | 3 | Date and version identifier | All pages |
| Funding | 4 | Sources and types of financial, material, and other support | Page 2 and 41 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | Page 16-17 |
| | 5b | Name and contact information for the trial sponsor | Page 16 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | Page 15 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | Page 17 |
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | Page 22 |
| | 6b | Explanation for choice of comparators | Page 23 |

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