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Study protocol for a multicentre, cluster randomised, superiority trial evaluating the impact of computerised 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. Computerised decision support systems (CDSSs) seem a promising tool to improve antimicrobial prescribing but have been insufficiently studied in clinical trials.

Methods and analysis The COMPuterized Antibiotic Stewardship Study trial, is a publicly funded, open-label, cluster randomised, controlled superiority trial which aims to determine whether a multimodal CDSS intervention integrated in the electronic health record (EHR) reduces overall antibiotic exposure in adult patients hospitalised in wards of two secondary and one tertiary care centre in Switzerland compared with ‘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 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 (Commission Cantonale d’Éthique de la Recherche (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; Pre-results.

INTRODUCTION

Inappropriate use of antimicrobials in hospitals is one of the key drivers of antimicrobial...
resistance (AMR) and Clostridium difficile infections (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 optimising patient outcomes.²

AMSS programmes 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 labour-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 programmes.

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 computerised decision support system (CDSS) at the time of prescribing.¹² CDSSs 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 6 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, multisite, comparative studies are critically needed to assist organisations 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 urinary tract infection¹⁶ and critically ill patients,¹⁷ and to improve empirical antibiotic treatment for patients with suspected bacterial infections.¹⁸ CDSSs are also often overly complex, poorly designed, not integrated into the workflow, expensive or difficult to implement in heterogeneous clinical settings.¹⁹

The COMPuterized Antibiotic Stewardship Study (COMPASS) trial aims to address this evidence gap by assessing through a randomised multicentre trial, if a CDSS integrated into the workflow can reduce days of therapy (DOT) per admission in the intervention wards compared with controlled wards, over a 1-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 1900 beds and 340 000 patient-days in acute care per year.²⁰ HUG has deployed an in-house electronic health record (EHR) since 2000 and a computerised physician order entry system (CPOE) system since 2006.²¹ ORL (Regional Hospital of Lugano) and OSG (Regional Hospital of 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 programmes 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 (eg, the intensive care unit and haematological or solid organ transplant wards), are also part of the AMS programme 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):

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.
4. Regular feedback of unit-wide antimicrobial prescribing indicators.

**Decision support for antimicrobial treatment**

When physicians prescribe a systemic antimicrobial agent (including antifungals and 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 prespecified 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. 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.

**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 (ie, if the alert is ignored by the prescriber the antimicrobial prescription will remain active), it will, however, continue to be displayed until it is addressed. The re-evaluation of treatment will be self-guided, that is, there will be no decision support guiding treatment adaptation based on patient-specific data such as vital signs, microbiological results or use of other medications. General information useful for re-evaluation, such as intravenous-oral switch criteria, will be provided as infobuttons. 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.

**Decision support for duration of treatment**

At the time of re-evaluation, the treatment duration will have to be entered. If the entered duration exceeds the duration proposed by the guidelines, a justification will have to be provided.

**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 emails outlining the performance of the ward compared to the other participating wards and compared with 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.
Control
The control will consist of routine, ‘standard-of-care’ AMS 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 an SD 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.

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 (eg, medicine, surgery, geriatrics) and baseline antibiotic use in 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, specialties may be matched across ORL and OSG since due to the smaller size these hospitals may only have one ward per specialty (eg, 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 (eg, orthopaedics or visceral surgery).

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 DOT of systemic antibiotic use per admission based on electronically recorded drug administration data (for details see table 2).23 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, microbiological outcomes, economic outcomes and user satisfaction (see table 2 for more detailed definitions).24 25

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 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.

Analysis
Outcome variables will first be summarised across treatment and intervention groups and then explored using descriptive statistics, taking into account the matched design by sandwich variance estimators for CIs. 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 vs 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 $R^2 > 0.8$.

**Data collection and management**

Most data will be retrieved from the hospital’s data warehouses. De-identified data will be stored in password-protected Microsoft Excel files on secured hospital servers. For the secondary outcome ‘qualitative assessment of antibiotic use’, an electronic Case Report Form (eCRF) will be created in an electronic data capture system such as Research Electronic Data Capture (REDCap Consortium).

For analysis data will be imported into a statistical programme, such as Stata V.15 (StataCorp) 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.
### Table 2  Main study outcomes and corresponding hypotheses evaluated within the COMPASS trial

| Outcome component | Relevant hypothesis (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* per admission. | DOT is an easily measurable, objectively assessable, outcome that is supported by expert consensus. Admission was chosen as the denominator for the primary outcome rather than PDs 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 PDs changes little despite a reduction in antibiotic exposure since both the numerator and denominator are reduced. |
| **Secondary outcomes: quantitative antimicrobial use†** | DOT per 100 patient-days (PD). Defined daily doses (DDD) per 100 PD and per admission. Antimicrobial days (ADs)‡ per 100 PD and per admission. Days per treatment period overall and for specific indications.§ | DDDs are the most widely used metric for antimicrobial consumption and are therefore most suitable for comparisons with other settings. ADs are a further metric that has been proposed to assess antibiotic use. Both PDs and admissions have been proposed as denominators. A treatment period is defined as antibiotic treatment not interrupted by more than one calendar day or discharge. |
| **Secondary outcomes: clinical outcomes** | Thirty-day mortality In hospital mortality. Unplanned hospital readmissions within Thirty days after discharge. Hospital LOS. Intensive or intermediate care unit admission from COMPASS wards. | The intervention is safe and does not result in an increase in mortality or readmissions. Similar LOS or a reduction in the LOS. No increase in the no of intensive care unit or intermediate care unit admissions. 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 are chosen based on their objectivity, the ease of obtaining the data and expert consensus. |
| **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. Switch to oral therapy when appropriate De-escalation of antimicrobial therapy by calendar day 4 of treatment Appropriate diagnostic exams. | 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. 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-month period) by infectious diseases specialists using prespecified criteria for appropriateness. A subselection of charts (about 10% of the sample) will be reviewed independently by two reviewers (blinded to ward assignment) to determine interobserver variability. |

Continued
### Outcome component

**Secondary outcomes: microbiological outcomes and healthcare-associated infections**

- **Incidence of healthcare facility-onset *Clostridium difficile*** denominated per 10 000 PD and admission (attributed to unit).
- **Incident clinical cultures with multidrug resistant organisms** (MRSA, ESBL-E, CPE, VRE, multidrug resistant *Pseudomonas aeruginosa*) denominated per 1000 PD and admission.

**Relevant hypothesis**

- Reduced incidence of healthcare facility-onset *C. difficile* infection (CDI).
- Reduced incidence of multidrug-resistant organisms.

**Rationale for outcome selection**

- Limiting 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.
- 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.

**Secondary outcomes: economic**

- Costs of administered antimicrobials (overall and by class) per admission and per admission receiving antibiotics.
- Costs of the intervention.
- Total costs of hospitalisation.

**Relevant hypothesis**

- Decreased overall direct costs for antimicrobials.

**Rationale for outcome selection**

- 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.
- All costs will be assessed from the perspective of the hospital.

**Other outcomes**

- Number of infectious diseases consultations.

**Relevant hypothesis**

- No difference in the number of infectious diseases consultations between the groups.

**Rationale for outcome selection**

- 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.

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*The primary outcome will be DOT for antibiotics belonging to Anatomical Therapeutic Chemical Classification System class J01 (anti-infectives for systemic use) plus oral metronidazole (P01AB01), oral vancomycin (A07AA09), rifampicin (J04AB02) and fidaxomicin (A07AA12).†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.‡The metric AD is equivalent to ‘length of therapy’.§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 analysed. CDSS, Computerised Decision Support System; COMPASS, COMPuterized Antibiotic Stewardship Study; CPE, carbapenemase-producing *Enterobacteriaceae*; ESBL-E, extended-spectrum beta-lactamase producing *Enterobacteriaceae*; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.*
ETHICS AND DISSEMINATION

A waiver of informed consent by prescribers and patients was 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 EHR 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. 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 feedback leveraging the potentials of the EHR. If effective, similar systems could be adapted in many hospitals given the relatively ‘simple’ design of the CDSS intervention.

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Contributors
BDH conceived the original idea for this study. BDH, GB, SH, BJ and RM secured funding for the study. BDH and GB 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: GC, MDK, BWS, RV, SH, LK, LE, RM, EB and BDH.

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Competing interests
None declared.

Patient consent
Not required.

Ethics approval
The trial has been approved by the competent ethics committees in Geneva and Ticino (CCER no 2017–00454).

Provenance and peer review
Not commissioned; peer reviewed for ethical and funding approval prior to submission.

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