BMJ Open

Effectiveness of the application of an electronic medication management support system in patients with polypharmacy in general practice: a study protocol of cluster-randomised controlled trial (AdAM)

Beate S Müller ,[1] Renate Klaaßen-Mielke,[2] Ana Isabel Gonzalez-Gonzalez ,[1,3] Daniel Grandt,[4] Reinhard Hammerschmidt,[5] Juliane Köberlein-Neu,[6] Petra Kellermann-Mühlhoff,[7] Hans J Trampisch,[2] Till Beckmann,[7] Lara Düvel,[7] Bastian Surmann,[8] Benno Flaig,[1] Peter Ihle,[9] Sara Söling,[10] Simone Grandt,[11] Truc Sophia Dinh,[1] Alexandra Piotrowski,[6] Ingo Meyer,[9] Ute Karbach,[12] Sebastian Harder,[13] Rafael Perera ,[14] Paul Glasziou ,[15] Holger Pfaff,[16] Wolfgang Greiner,[8] Ferdinand M Gerlach,[1] Nina Timmesfeld,[2] Christiane Muth ,[1,17] AdAM study group

To cite: Müller BS, Klaaßen-Mielke R, Gonzalez-Gonzalez AI, *et al*. Effectiveness of the application of an electronic medication management support system in patients with polypharmacy in general practice: a study protocol of cluster-randomised controlled trial (AdAM). *BMJ Open* 2021;**11**:e048191. doi:10.1136/bmjopen-2020-048191

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-048191).

BSM and RK-M are joint first authors.

Received 18 December 2020
Accepted 10 September 2021

For numbered affiliations see end of article.

Correspondence to
Dr Ana Isabel Gonzalez-Gonzalez; gonzalezgonzalez@allgemeinmedizin.uni-frankfurt.de

ABSTRACT

Introduction Clinically complex patients often require multiple medications. Polypharmacy is associated with inappropriate prescriptions, which may lead to negative outcomes. Few effective tools are available to help physicians optimise patient medication. This study assesses whether an electronic medication management support system (eMMa) reduces hospitalisation and mortality and improves prescription quality/safety in patients with polypharmacy.

Methods and analysis Planned design: pragmatic, parallel cluster-randomised controlled trial; general practices as randomisation unit; patients as analysis unit. As practice recruitment was poor, we included additional data to our primary endpoint analysis for practices and quarters from October 2017 to March 2021. Since randomisation was performed in waves, final study design corresponds to a stepped-wedge design with open cohort and step-length of one quarter. Scope: general practices, Westphalia-Lippe (Germany), caring for BARMER health fund-covered patients. Population: patients (≥18 years) with polypharmacy (≥5 prescriptions). Sample size: initially, 32 patients from each of 539 practices were required for each study arm (17 200 patients/arm), but only 688 practices were randomised after 2 years of recruitment. Design change ensures that 80% power is nonetheless achieved. Intervention: complex intervention eMMa. Follow-up: at least five quarters/cluster (practice). recruitment: practices recruited/randomised at different times; after follow-up, control group practices may access eMMa. Outcomes: primary endpoint is all-cause mortality and hospitalisation; secondary endpoints are number of potentially inappropriate medications, cause-specific hospitalisation preceded by high-risk prescribing and medication underuse. Statistical analysis: primary and secondary outcomes are measured quarterly at patient level. A generalised linear mixed-effect model and repeated patient measurements are used to consider patient clusters within practices. Time and intervention group are considered fixed factors; variation between practices and patients is fitted as random effects. Intention-to-treat principle is used to analyse primary and key secondary endpoints.

Ethics and dissemination Trial approved by Ethics Commission of North-Rhine Medical Association. Results

Strengths and limitations of this study

- We will provide evidence of the effectiveness of an electronic medication management support system in reducing mortality and hospitalisation in adult patients with polypharmacy in real-life general practice.
- The intervention concept is innovative, as it is the first time that information based on claims data is made available to general practitioners (in Germany) in the form of an electronic tool.
- However, claims-based outcome measures also have disadvantages, as data are collected for the purpose of reimbursement, which limits the choice of outcomes.
- A stepped-wedge cluster-randomised design with an open cohort will allow us to overcome insufficient recruitment.
- We included a time variable to adjust for confounding time effects and overcome such methodological shortcomings of stepped-wedge design.

will be disseminated through workshops, peer-reviewed publications, local and international conferences.

Trial registration NCT03430336. ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT03430336).

INTRODUCTION

Multiple medications are often required to manage clinically complex patients. Clinicians are frequently challenged by the need to ensure that treatment of complex patients adheres to disease-specific clinical practice guidelines.

Polypharmacy, defined as the use of five or more medications,[1] increases the potential for the prescription of potentially inappropriate medications (PIMs) due to the non-consideration of drug–drug or drug–disease interactions, inappropriate dosages (perhaps due to the age of the patient) as well as unintended duplicate prescriptions.[2–6] The use of greater numbers of drug therapies has been associated with increased risk of adverse drug reactions[7] irrespective of age.[8] It has also been associated with increased risk of hospital admissions,[9–11] hip fractures in older adults[12] and higher costs and mortality.[10 11 13]

In line with the increasing number and complexity of medications, polypharmacy is associated with reduced medication adherence in patients. It may also result in undertreatment, particularly in the elderly, in whom too few prescriptions and excessively low dosages have been reported.[14–16]

Medication errors and omissions are important problems facing routine care in general practice, especially in patients with multimorbidity and multiple prescriptions.[17–19] They may contribute to patient hospital admissions and mortality, thus additional understanding of such incidents is required.[20] As most medication errors and omissions are preventable, raising physicians' awareness of polypharmacy may help to ensure the safe, effective and appropriate use of medication.[19 21 22]

Medication management strategies allow patients and families to actively participate with their physicians in developing complete and accurate medication lists. To ensure patients receive high-quality healthcare, physicians should be provided with tools that help them avoid risks in the treatment of their patients.[22–24] Likewise, physicians should have access to continuously available data on quality-oriented aspects to support the control of their patients' treatments.[24] Few effective instruments are available to help physicians systematically monitor and optimise the medications their patients take.[22] Such tools comprise computerised Decision Support Systems (CDSS) or complex multifaceted pharmaceutical care-based approaches that may incorporate CDSS as part of the intervention. CDSS are computer-based systems providing 'passive and active referential information as well as reminders, alerts and guidelines'.[25] A recent systematic review[26] concluded that although CDSS may reduce PIMs, additional randomised controlled trials are needed to assess their impact on patient-relevant outcomes and to evaluate the use of medication targets such as the Screening Tool of Older People's Prescriptions and the Screening Tool to Alert doctors to the Right Treatment (START) criteria.[27]

Considering that individual, patient-related information relevant for the drug therapy is currently unavailable to physicians and that there is a lack of instruments helping physicians to regularly review their patients' medication, an intervention with a web-based medication management system was developed within the Anwendung für digital unterstütztes Arzneimitteltherapie-Management (AdAM) project. The primary objective of the AdAM trial is, therefore, to assess whether such electronic medication management support system (complex intervention) reduces the combined endpoint of all-cause mortality and all-cause hospital admissions in patients with polypharmacy, compared with usual care and in the real context of a general practice setting. Substudies to be performed will include cost-effectiveness analysis, the analysis of barriers and facilitators through interviews and focus groups with practitioners and interviews with patients, a trial process evaluation as well as sustainability analysis and quality cost accounting systems to explore the relationship between organisational context, implementation process and quality of care (online supplemental additional file 1). However, as this study protocol focuses on the AdAM intervention, these substudies will not be explained in detail in this paper.

AIMS

The AdAM trial aims to:

1. Evaluate whether the complex intervention reduces the combined outcome of all-cause hospitalisation (including night-only and day-only admissions) and all-cause mortality (primary outcome) or any of its components (secondary outcomes) in patients with polypharmacy, compared with usual care.
2. Evaluate whether the complex intervention reduces cause-specific hospitalisation preceded by high-risk prescribing in patients with polypharmacy, compared with usual care (secondary outcomes).
3. Ascertain whether the complex intervention reduces the number of PIMs and Potential Prescribing Omissions as measured using explicit criteria, in patients with polypharmacy, compared with usual care (outcomes of process of care).
4. Assess whether the complex intervention reduces the number of prescribed medications in patients with polypharmacy, compared with usual care (outcomes of process of care).
5. Evaluate whether the complex intervention is effective in reducing the combined primary outcome, or any of its components, in subgroups of patients defined according to age (<65 vs ≥65 years), sex, early and late enrolment (patient does or does not fulfil the inclusion criteria from the moment he or she joins the intervention of the associated practice) and main treating

physician (general practitioner—GP vs specialised physician or hospital outpatient clinics).

METHODS AND ANALYSIS

Study design

The AdAM trial was originally planned as a pragmatic, parallel cluster-randomised controlled trial (cRCT) with 15 months (five quarters) of follow-up per cluster (practice). The general practice was the unit of randomisation and the patient the unit of analysis. Since GPs trained in performing the intervention are unable to provide usual care, a clustered design (practices as clusters) was chosen to reduce treatment group contamination.

Important changes after trial launch

When practice recruitment ended in June 2019, it became obvious that the target numbers of practices and patients would not be achieved. Extensive simulations were, therefore, conducted on the assumptions that the number of eligible patients was the same (39 per practice) in all 688 randomised practices, that 60% of potential patients had enrolled and that the event rate in the control group would be constant in all quarters. After completing the simulation, we decided to change the design of the trial in such a way that a power of 80% could still be reached. The following changes were made and will be explained in detail in each section of the protocol: (1) primary and secondary outcomes will be measured at regular intervals over 12 quarters, rather than once after five quarters and (2) The statistical analysis will be adapted to take account of the new design.

All changes were made before data from the study population were analysed (figure 1).

Study setting and population

The trial is conducted in general practices in Westphalia-Lippe, Germany.

Inclusion criteria for trial sites (general practices)

All criteria had to be fulfilled:

- General practices provide health services to patients covered by the BARMER statutory health insurance fund (BARMER).

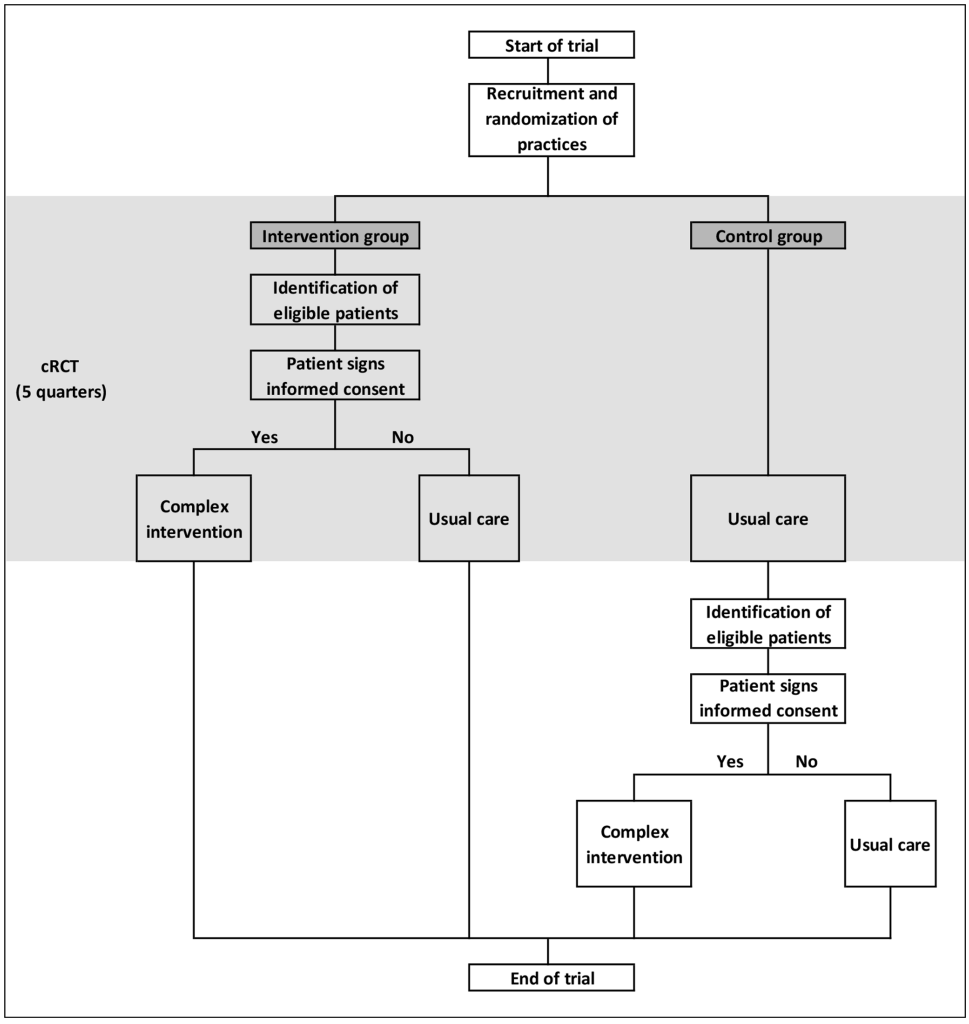

Figure 1 AdAM study flowchart. AdAM, Anwendung für digital unterstütztes Arzneimitteltherapie-Management; cRCT, cluster-randomised controlled trial.

- Physicians work as GPs and have specialised in general practice, internal medicine or in no particular field.
- Practices have at least 10 eligible patients.
- Practices have access to the Westphalia-Lippe Association of Statutory Health Insurance Physicians (KVWL) website through a secure connection that can be used by both GPs and other medical staff (practice nurse and healthcare assistants).
- Investigators agree to fulfil the contractual obligations arising from the trial.

Inclusion criteria for patients

All criteria had to be fulfilled:

- Patients are at least 18 years of age and covered by BARMER.
- They have polypharmacy, defined as the regular intake of at least five drugs (≥ five different Anatomical Therapeutic Chemicals—ATC) in at least one quarter of the previous year. Each of the five ATCs has to be prescribed over at least two consecutive quarter in the previous year.

In order to participate in the intervention, patients had to provide written informed consent (online supplemental additional file 2). They also had to be competent to sign the required documents under law and capable of providing written informed consent to participate in the trial voluntarily. Patients who were not competent to sign the documents under law and were not capable of providing written informed consent to participate in the trial voluntarily (eg, because of dementia) could provide written informed consent signed by an informal caregiver.

No changes were made to setting and study population after trial launch

Recruitment and registration

Recruitment and registration of practices

The KVWL and the BARMER provided a list of general practices that were eligible to participate in the trial. Of these, the KVWL contacted GPs from practices with at least 10 eligible patients by postal mail (written invitation). Reminders were later sent by fax. GPs who wished to participate had to return a signed investigator's agreement form to the KVWL (either by postal mail or fax).

Moreover, the trial was announced in journals and local media (press, radio, television) and communicated to local key stakeholders (moderators of quality circles, managers of practice networks, etc). Local recruitment events were also organised.

Recruitment and registration of patients

STEP 1: before randomisation and quarterly during the intervention period, the BARMER identified eligible patients from the participating general practices based on claims data.

STEP 2: after cluster-randomisation of participating practices, patients in the intervention practices were recruited in three ways:

- Every quarter, GPs received a list of eligible patients as well as written information and informed consent forms for the patients. The GPs could, therefore, invite eligible patients on their lists to participate.
- The BARMER sent written information on the study (information letter and a flyer) to eligible patients from participating intervention practices, so that they could actively approach their GPs to find out about the study. The aim was to explain the contents of the AdAM project to eligible patients in good time in order to arouse interest and actively assist in enrolment. The BARMER telephone hotline was available to immediately answer any questions the patients had. Additional information on the study was provided on the BARMER website (daily news and Frequently Asked Questions (FAQ) list).
- GPs invited patients from their practices that fulfilled the inclusion criteria but had not (yet) been identified as eligible from claims data (eg, due to a delay of data processing).

STEP 3: GPs sent patients' written informed consent to the KVWL. The KVWL digitised the consent forms and transmitted them to BARMER for verification of insurance status. When the results were positive, KVWL permitted GPs to access the electronic medication management support system (eMMa) and forwarded the original consent forms to the BARMER for archiving.

When the follow-up period of the cRCT was over, eligible patients in the control group that were identified in STEP 1 were invited to provide their written informed consent and participate in the intervention. Beginning with STEP 2, the recruitment and registration of control patients followed the same procedure as intervention patients (figure 1).

No changes were made in recruitment and registration after the trial began

Randomisation and allocation concealment

Practices were randomly allocated to the complex intervention or control arm in a ratio of 1:1 (figure 2). Balanced randomisation was performed every month to ensure that the treatment groups were of approximately equal size for each quarter. The KVWL provided lists of participating practices to the Department of Medical Informatics, Biometry and Epidemiology (AMIB) at the Ruhr University Bochum, Germany. A study-independent staff member at the AMIB used computer-generated random numbers to generate randomisation lists from the list of participating practices. Randomisation lists were sent to KVWL, which concealed treatment allocation to participating practices. Once a practice was randomised, all eligible patients at the practice were deemed to be intervention or control patients, depending on the arm of the study the practice was allocated to. The first list of eligible patients in the intervention group was made available to participating physicians and the intervention began, after patients had signed the informed consent form. Eligible patients in the control group continued to receive usual

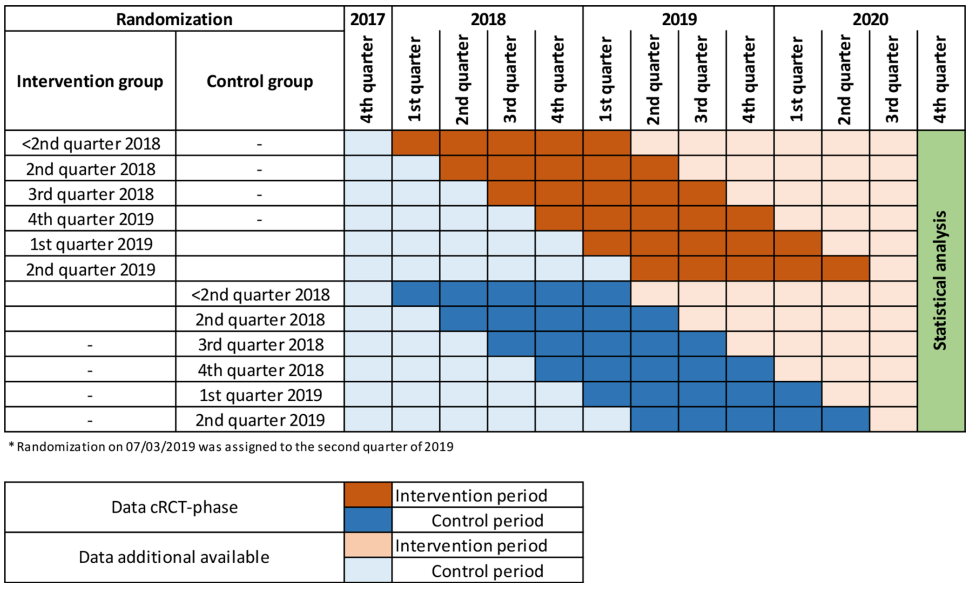

Figure 2 AdAM data availability (time flow). AdAM, Anwendung für digital unterstütztes Arzneimitteltherapie-Management; cRCT, cluster-randomised controlled trial.

care. After signing the informed consent form, eligible patients in the control group were invited to participate in the intervention five quarters after the start of the intervention at the other practices from the same randomisation wave.

No changes were made in randomisation and allocation concealment after the trial began

Blinding

Allocation was disclosed to the practices soon after randomisation and to patients from intervention practices when they were asked to provide their written informed consent. Patients in the control group were not aware of the study until the end of their practice's follow-up period of the cRCT.

Due to the type of intervention, neither GPs and their patients nor the AdAM study team was blinded to the treatment allocation.

No changes were made in blinding after trial commencement

Treatment plan for intervention and control groups

Intervention group

Several key elements of the intervention must be put into place in participating general practices:

1. The web-based, user-initiated CDSS eMMa provides the GP with drug–therapy information that is relevant to participating patients with polypharmacy on demand. The information might include data on diagnoses, treatments (also non-pharmacologic, such as physiotherapy) and medical products (eg, assistive devices). The information is based on claims data gathered from all healthcare professionals involved in the care of the patient (eg, specialised ambulatory care physicians, other GPs, psychotherapists as well as data on hospital stays and prescription data from pharmacies). RpDoc Solutions GmbH developed eMMa in collaboration with KVWL.
2. GPs can add and modify patient data in eMMa (eg, remove drugs that the patient no longer takes, add new diagnoses, prescriptions and over the counter (OTC) drugs and recent laboratory findings about kidney function, etc) in order to enhance and update relevant information.
3. Aided by eMMa, GPs systematically assess the appropriateness of every patient's medication at least once a year. Alerts will draw the GP's attention to possible drug–drug interactions, drug–disease interactions, age-related PIMs, duplicate medications, renal dose adjustments, allergies, as well as general inappropriateness, such as prescriptions associated with Dear Doctor letters (Rote-Hand-Briefe) and QT prolongation (for a detailed description see online supplemental additional file 3).
4. GPs optimise patient medication.
5. GPs print out the updated medication plan, which includes recommendations on medication use, reasons for prescriptions in lay language, and information on drugs that should be avoided, and hand it out to patients. The plan will also be available in foreign languages for patients that speak poor German.
6. eMMa provides GPs with guidance (eg, recommendations addressing certain types of medication errors and high-risk prescribing that were developed by the German Society for Internal Medicine in collaboration with other scientific medical societies).

Intervention training

GPs were invited to attend two kick-off meetings and a decentralised event on polypharmacy with a consulting pharmacist from KVWL.

Table 1 Primary outcome measure—CPO—all-cause mortality and all-cause hospitalisation

Number	Outcome
CPO-1	All-cause mortality and all-cause hospitalisation (including emergency admissions).

CPO, composite primary outcome.

GPs and healthcare assistants also could attend a decentralised software training event with consulting pharmacists and IT support staff.

The KVWL has made a training video and an FAQ list for participating practices available on the trial access site.

During practice hours, several telephone hotlines were offered for technical questions (IT support) and to provide on-site support for questions relating to administration, management and use.

The Template for Intervention Description and Replication (TIDieR) checklist was used to ensure that the intervention reporting standards were met (online supplemental additional file 4).

No changes were made to the experimental treatment after the trial commenced.

Control group

For the duration of the cRCT, patients in the control group continued to receive usual treatment from their GP. Five quarters after the start of the intervention at the other practices from the same randomisation wave, control practices could switch to intervention and the patients in these practices had the option to switch to the intervention group on condition that they first provide their written informed consent to receive the intervention.

No changes were made concerning the control group, as the switch to the intervention group was already planned in order to carry out the substudy on sustainability (see online supplemental additional file 1).

Outcome assessment

Primary outcome

The primary outcome is the combined endpoint of all-cause mortality and all-cause hospitalisation (including night-only and day-only admissions) in patients with polypharmacy, as assessed quarterly (table 1).

Secondary outcomes

1. All-cause hospitalisation (quarterly): to evaluate whether the complex intervention reduces all-cause hospitalisation (including day-only or night-only admissions) (number and duration) in patients with polypharmacy (table 2).

Table 2 Secondary outcome measures—hospitalisation* (SOh)

Number	Outcome
SOh-1	All-cause hospitalisation.

*Hospitalisation includes day and night admissions (emergency admissions) combined and separately.

Table 3 Secondary outcome measure—mortality (SOm)

Number	Outcome
SOm-1	All-cause mortality.

2. All-cause mortality (quarterly): to assess whether the complex intervention reduces all-cause mortality in patients with polypharmacy (table 3).

3. Incidence rate of cause-specific hospitalisation preceded by high-risk prescribing (quarterly): to evaluate whether the complex intervention reduces cause-specific hospital admissions (gastrointestinal bleeding, heart failure, renal failure, fall-related fractures or injuries; including and excluding day-only admissions) preceded by high-risk prescribing in patients with polypharmacy (table 4).

Secondary outcomes concerning process of care

4. Number of PIMs (quarterly): to ascertain whether the complex intervention improves the appropriateness of prescriptions in patients with polypharmacy (tables 5 and 6).

5. Total number of underused medications (quarterly): to assess whether the total number of underused medications (based on the modified START criteria) in patients with polypharmacy does not increase in the intervention group in comparison to the control group (table 7).

6. Total number of prescribed medications (quarterly): To assess whether the complex intervention reduces the total number of prescribed medications in patients with polypharmacy (table 8).

Data for primary and secondary outcomes will be taken from health insurance claims data (BARMER) for the period from the fourth quarter 2017 to the first quarter 2021.

Changes made after trial commencement: initially, we planned a one-time survey of outcomes for a period of five quarters following randomisation. In the end, data on the endpoints were collected quarterly for the period from the fourth quarter 2017 to the first quarter 2021.

See online supplemental additional file 5 for more information about the secondary outcome measures.

Explanatory variables for population characteristics

Patient (first level) variables

- Sociodemographic patient data: sex, age, insurance status and reason insurance coverage ended (death, change of sickness fund).
- Outpatient diagnoses and outpatient services: the International Classification of Diseases 10th edition codes[28] are used for the outpatient diagnoses, which are documented on a quarterly basis. The services are coded according to the Physician's Fee Scale (Einheitlicher Bewertungsmaßstab).
- Medication: drugs are identified using their national drug code (pharmaceutical registration number,

Table 4 Secondary outcome measures—cause-specific hospital admissions (SOh)

Number	Outcomes
Cause-specific hospital admissions preceded by high-risk prescribing	
SOh-2	Hospital admissions due to GI bleeding or ulcers in patients at risk for medication-related GI disorders (defined in SOpim 1–8 measures) in the 12 weeks before admission.[33]
SOh-3	Hospital admissions due to acute heart failure or acute renal failure in patients at risk for medication-related cardiovascular disorders (defined in SOpim 9–17 measures) in the 12 weeks before admission.[33]
SOh-4	Hospital admissions due to fall-related fractures or injuries in patients who were at risk for medication-related falls (defined in SOpim 18–19 measures) in the 12 weeks before admission.
Cause-specific hospital admissions not preceded by high-risk prescribing	
SOh-5	Hospital admissions due to GI bleeding or ulcer in patients who were not at risk for medication-related GI disorders (defined in SOpim 1–8 measures) in the 12 weeks before admission.
SOh-6	Hospital admissions due to acute heart failure or acute renal failure in patients who were not at risk for medication-related cardiovascular disorders (defined in SOpim 9–17 measures) in the 12 weeks before admission.
SOh-7	Hospital admissions due to fall-related fractures or injuries in patients who were not at risk for medication-related falls (defined in SOpim 18–19 measures) in the 12 weeks before admission.

Pharma-Zentral-Nummer—PZN), which contains all relevant information such as trade name, active chemical ingredient(s), strength, application, dosage and indication. The PZN will be linked to the ATC Classification System, which allows analysis to be based on active ingredients, manufacturer and package

Table 5 Secondary outcome measures—PIM-related high-risk prescribing (SOpim)

Number	Outcomes
High risk of GI bleeding	
SOpim-1	Patients with a peptic ulcer, GERD, Crohn's disease or gastritis who were prescribed a traditional oral NSAID* without a gastroprotective drug.[33 34]
SOpim-2	Patients aged ≥65 who were prescribed a traditional oral NSAID* without a gastroprotective drug.[33]
SOpim-3	Patients prescribed a platelet aggregation inhibitor excluding heparin and a traditional oral NSAID* without a gastroprotective drug.[33 34]
SOpim-4	Patients prescribed a fixed combination of aspirin and clopidogrel or aspirin and either clopidogrel, ticagrelor or prasugrel without a gastroprotective drug.[33]
SOpim-5	Patients prescribed an oral anticoagulant or a direct thrombin inhibitor or a direct factor Xa inhibitor and a traditional oral NSAID* without a gastroprotective drug.[33 34]
SOpim-6	Patients prescribed an oral anticoagulant and a platelet aggregation inhibitor excluding heparin without a gastroprotective drug.[33 34]
SOpim-7	Patients prescribed SSRI or SSNRI with a traditional oral NSAID* without a gastroprotective drug.[35 36]
SOpim-8	Patients prescribed a systemic glucocorticoid with a traditional oral NSAID* without a gastroprotective drug.[35]
High-risk cardiovascular prescribing	
SOpim-9	Patients prescribed an ACE inhibitor/ARB/renin inhibitor with an oral NSAID*.[33 34]
SOpim-10	Patients prescribed a diuretic with an oral NSAID*.[33 34]
SOpim -11	Patients with heart failure prescribed any oral NSAID*.[33 34]
SOpim-12	Patients with heart failure prescribed a tricycle antidepressant.[35 37]
SOpim-13	Patients prescribed an ACE inhibitor/ARB/renin inhibitor or a potassium-sparing diuretic including aldosterone antagonists with a potassium supplement.[34 35 37]
SOpim-14	Patients with heart failure prescribed a beta-blocking agent, non-selective.[37]
SOpim-15	Patients aged ≥65 prescribed a QTc prolongation drug.[38 39]
SOpim-16	Patients prescribed two or more QTc prolongation drugs or a QTc prolongation drug with an inhibitor of its isozyme (CYP3A4, CYP2D6) or with known risk factors (heart failure, bradycardia, sick sinus syndrome including tachycardia-bradycardia syndrome, other cardiac arrhythmias including long-QT syndrome).[38 39]
SOpim-17	Patients prescribed digitalis glycosides with a non-potassium-sparing diuretic and no potassium supplement.[34]
High-risk prescribing with regards to falls	
SOpim-18	Patients aged ≥65 prescribed a drug that increases risk of falling.[38]
SOpim-19 a/b	Patients with Parkinson's disease or other degenerative diseases of basal ganglia prescribed a drug that increases risk of falling.[38]

High-risk prescribing is related to prescriptions in the previous 12 weeks.
*Information related to NSAID is based on claims data; over-the-counter medications cannot be measured.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GERD, gastroesophageal reflux disease; NSAID, non-steroidal anti-inflammatory drug; QTc, corrected QT interval; SRNI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitor.

Table 6 Secondary outcome measures—PIM-related high-risk prescribing composite (SOpim)

Number	Outcomes	
High-risk prescribing composite		
SOpim-20	Patients with any risk factor and one or more high-risk prescriptions as defined in SOpim measures 1–8.	GI risk composite
SOpim-21	Patients with any risk factor and one or more high-risk prescriptions as defined in SOpim measures 9–17.	V risk composite
SOpim-22	Patients with any risk factor and one or more high-risk prescriptions as defined in SOpim measures 18–19.	Fall risk composite
SOpim-C	Patients with any risk factor and one or more high-risk prescriptions as defined in SOpim measures 20–22.	High-risk prescription
Initiation and discontinuation prescription measures		
SOpim-Ci	Patients who were not exposed to high-risk prescriptions (as defined in SOpim-C measures) in the 12 weeks previous to the intervention (as defined by date of the intervention invoice) and who received a high-risk prescription (as defined in SOpim-C measures) within 12 weeks of the beginning of the intervention.	Initiation of high-risk prescriptions
SOpim-Cd	Patients who were exposed to a high-risk prescription (as defined in SOpim-C measure) in the 12 weeks previous to the intervention (as defined by date of the intervention invoice) that did not receive a high-risk prescription within 12 weeks of the beginning of the intervention.	Discontinuation of high-risk prescriptions

CV, cardiovascular; PIM, potentially inappropriate medication.

size. The duration of the therapy will be assessed by means of the defined daily dose and included in the reference table. The data set only includes prescribed medication that is paid for by the insurance fund.

- Inpatient data: for each hospitalisation, the start and end date, the admission and discharge diagnosis (with date), as well as secondary diagnoses, will be available. Furthermore, operations and treatment procedures are also documented (Operation and Procedure—Code).
- Long-term nursing care (Sozialgesetzbuch): for patients receiving long-term nursing care, the start and end date, the level and place of care, the costs and type of services (cash, non-cash, combined) are documented in the data set.

Practice profile (second level) variables

- Single-handed practice/group practice (including ambulatory healthcare centres, along with the number of physicians).
- Work experience (start and end date of practice according to KVWL data).
- Practice size: number of registered patients in most recent quarter.
- Participation in a (regional) practice network.

GP profile (second level) variables

- Age, gender.

No changes were made to explanatory variables

Safety monitoring and adverse events

Safety and adverse events were not monitored and reported on, since it was assumed that treatment could not deteriorate as a result of the trial. The study team had no influence on the diagnostic–therapeutic decision-making of GPs and their patients, and analysis of the pseudonymous data will be conducted with a significant delay. GPs and patients could, therefore, not be informed of identified medication errors.

Table 7 Secondary outcome measures—underused medication (SOum)

Number	Outcomes
Underused medication	
SOum-1	Patients with chronic atrial fibrillation who were not prescribed vitamin K antagonists or direct thrombin inhibitors or direct factor Xa inhibitors in the previous 12 weeks.[27]
SOum-2	Patients with coronary, cerebral or peripheral vascular disease who were not prescribed an antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor).[27]
SOum-3	Patients with ischaemic heart disease who were not prescribed a beta-blocker.[27]
SOum-4	Patients who were prescribed methotrexate without a folic acid supplement in) the previous 12 weeks.[27]
SOum-5	Patients who were receiving opioids regularly without laxatives in the previous 12 weeks.[27]
SOum-6	Patients with systolic heart failure and/or documented coronary artery disease who were not prescribed ACE inhibitors or ARB.[27]
SOum-7	Patients with stable systolic heart failure who did not receive appropriate beta-blockers (bisoprolol, nebivolol, metoprolol or carvedilol).[27]
SOum-8	Patients not regularly taking an inhaled β2 agonist or antimuscarinic bronchodilator for mild to moderate asthma or COPD.[27]
SOum-9	Patients not regularly taking an inhaled corticosteroid for moderate-severe asthma or COPD.[27]
SOum-10	Patients with diabetes with or without serum biochemical renal impairment who did not receive ACE inhibitors or ARB (if intolerant of ACE inhibitors).[27]

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Table 8 Secondary outcome measures and process measures—polypharmacy indicators (SOp)

Number	Outcomes
SOp-1	Number of prescriptions per patient

Testing of these outcomes will be exploratory.

Unintended consequences of using the e-Health technology such as non-acceptance will be investigated qualitatively (online supplemental additional file 1).

Data collection and management

Data collection

Information on all eligible patients was taken pseudonymously from BARMER's claims data. Claims data detail billable interactions (insurer claims) between the insured patients and the healthcare delivery system.

In the trial, the KVWL data are not systematically linked to BARMER's data on either a practitioner or patient level. The KVWL provides sociodemographic data on GPs and practice profiles for both the intervention and control groups.

Data management

The required claims data for all eligible patients in the region covered by the KVWL will be specified in a coordinated Minimum Data Set (MDS) and prepared by the PMV research group in Cologne.

The trial data will be archived for 10 years. BARMER will archive a back-up copy containing the data of all study patients (list of eligible patients, declarations of consent to participate in the trial and on data protection, signed and dated by the patients as well as the data provided for the evaluation) in accordance with European basic data protection regulations. The KVWL will archive documents concerning the general practices/GPs participating in the trial (eg, signed investigator's agreement form). The Institute of General Practice (IGP) will archive the trial master file and any related study plans (MDS and statistical analysis plan). The data provided by KVWL and eMMa, as well as primary data collected in interviews with patients, will be archived by the IGP in accordance with European basic data protection regulations.

End of the trial

The regular end of the intervention and follow-up period for all patients was March 2021.

A patient's participation in the intervention ends prematurely: (1) when he or she switches to another insurance company and/or a non-participating practice or (2) the GP withdraws his or her consent or is no longer licensed to provide health services by the KVWL.

Schedule and duration of the trial

Practice recruitment: 2 May 2017 to 30 June 2019.

Intervention period: 15 February 2018 to 31 March 2021.

Claims data from 1 January 2017 to 31 March 2021 will be used in the analysis. The cohort is open, meaning that patient data are included from the quarter in which the inclusion criteria are met.

Quality control and quality assurance

The principal investigator and a steering committee (comprising representatives of BARMER, KVWL and the evaluation team) guarantee that all processes in the trial comply with Good Clinical Practice (GCP) guidelines and ethical and legal requirements.

BARMER and the KVWL are responsible for monitoring the trial and were in particular responsible for the recruitment of practices and patients, randomisation (supported by the AMIB), the implementation of the intervention and the provision of data to the evaluation team.

A designated advisory board provides advice on questions concerning planning, conducting and analysing the trial.

Changes to data collection and data management: initially, data collection for each practice was to be carried out as a one-time survey to take place after the start of randomisation and over a period of five quarters. In the end, data were collected at regular intervals over 12 quarters from the fourth quarter 2017 to the first quarter 2021 (light blue and light red areas in figure 2).

Sample size

Initially, based on data detailing the incidence of hospitalisation and all-cause mortality in patients with multiple prescriptions, we expected rates of 30% in the control group over a 12-month follow-up period.[16 17] Based on a duration of 15 months (five quarters), the rates were assumed to be 35.25% in the control group, with a relative reduction of 5% in the intervention group. Based on 80% recruitment of practices and patients and an intra-cluster correlation coefficient of 1%, a sample size of 17 200 cluster-randomised patients per group (539 practices per study arm, about 32 patients per practice) is required to detect an absolute difference in the combined endpoint of 1.8% between intervention and control groups (type 1 error of 5% and type 2 error of 15%).

Changes made after trial launch: at the end of practice recruitment in June 2019, it became clear that the target numbers of practices could not be achieved. In the period from 27 June 2017 to 03 July 2019, 688 practices were randomised to the intervention and control groups. Based on the assumptions of 26 832 (688*39) eligible patients in the randomised practices, a participation rate of 60% of patients in the intervention group, the same number of practices at all changeover times (ie, the switch from control to intervention group) and a constant event rate in the control group over all quarters, a power of 80% is achievable.

Statistical analysis

Population for analysis

As both patients who met the inclusion and exclusion criteria from the beginning and patients who fulfilled

the inclusion and exclusion criteria after the trial had commenced were able to receive the intervention, the ITT population was an open cohort. Patients from participating practices, therefore, started from the time at which inclusion and exclusion criteria were met during a period stretching from the fourth quarter 2017 to the end of the first quarter 2021. Following the ITT principle, practices and their patients will be analysed quarterly, according to the group to which the practice was allocated, regardless of whether they refused or discontinued the allocated treatment, or whether there were other deviations from the protocol.

For the efficacy analysis, only patients who were selected from the intervention group and for whom the GP had performed the intervention will be considered. This subgroup will be compared with patients in the control group that started the intervention after completion of the cRCT phase. In this population, it will be possible to estimate the maximum possible effect of the intervention, comparable to a per-protocol population.

No changes were made to the population for analysis.

Statistical hypotheses, methods and analyses

The primary objective of this study is to determine whether the complex intervention reduces the combined endpoint of all-cause mortality and all-cause hospitalisation (including night-only and day-only admissions) in adult patients with polypharmacy, as compared with usual care. Statistically, the study objective is formulated as a test of the null hypothesis H0: p1=p2 (the two groups do not differ in terms of the quarterly event probability of combined endpoint pi, where i=1 or 2 for intervention or control group, respectively), compared with the alternative hypothesis H1: p1≠p2 (there is a difference between the two groups).

The analysis is based on quarterly data at a patient level and patients are clustered in practices. We will adjust for the different observation periods and for clustering in the data by fitting an appropriate generalised linear mixed model (GLMM). A mixed logistic regression model will, therefore, be used for all binary outcomes, and especially for the primary endpoint.

Time and treatment group and further confounders such as age, sex, the medCDS prognostic index,[29] care level/degree at baseline, days in hospital in the 12 months preceding baseline are considered to be fixed factors. Since all practices were observed under both control and intervention conditions, it will be necessary to include two correlate random cluster-level effects in the model. To gauge the interdependence of individual measurements OTC of the study, additional uncorrelated random effects for patients will also be fitted.

In the AdAM trial, we have assumed that the intervention requires an initial period of adjustment before becoming fully embedded. The intervention effect is, therefore, expected to gradually increase from the time the practice switches to the intervention (¼ in the quarter of the practice change, ½ in the quarter after the change to intervention and the full effect thereafter).

A similar approach will be used to investigate secondary outcomes, sensitivity and efficacy.

The secondary outcomes 2 (all-cause hospitalisation) and 3 (all-cause mortality) are to be analysed hierarchically, reflecting the rationale of the intervention, with a significant decrease in the combined primary endpoint of all-cause mortality and all-cause hospital admissions (level 1) expected to reflect primarily in a decline in all-cause hospitalisation (level 2). If so, all-cause mortality may also decrease (level 3). Therefore, the prespecified secondary outcomes 2 and 3 will be tested in a confirmatory manner. If no significant differences occur at any level, tests of outcomes on higher levels will be exploratory.

The baseline characteristics of participating practices, GPs and patients will be described according to the initially allocated treatment arm. Categorical data will be presented as frequencies and percentages. Total numbers, mean, SD, median, IQR, minimum and maximum will be provided for continuous data.

All statistical tests will be two sided at a significance level of α=0.05. No interim analysis of efficacy will be performed.

Changes made after trial launch: we initially planned to use a GLMM to evaluate the treatment effect in a randomised parallel group design. In addition to considering the treatment group to be a fixed factor, a random effect to account for clustering patients in practices is necessary. Due to the switch to a stepped-wedge design, a more complex model structure was required (see above).

Patient and public involvement

This protocol was developed without patient or public involvement.

ETHICS AND DISSEMINATION

The project is being carried out in accordance with the Medical Association's code of conduct and GCP, and in line with the World Medical Association Declaration of Helsinki.[30] The study plans and all patient-related documents have been sent to and approved by the Ethics Commission of the North-Rhine Medical Association (approval date 26 July 2017, approval number 2017184).

All changes made and reported here after the trial began have also been sent to and approved by the abovementioned ethics committee (approval date 3 April 2020, approval number 6000207769).

The voluntary participation of practitioners in the trial is recorded in writing following their informed decision. Patients were asked for their consent as soon as the practice switched to the intervention. Patients who did not wish to participate continued to receive usual care.

Data protection is guaranteed for all patient-related data. Eligible patients were identified using pseudonymous claims data from BARMER, whereby BARMER previously informed the patient of the opportunity to

participate in the trial. Before the intervention began, patients were separately informed about data protection during the trial and intervention. Patients had to provide their informed consent by signing and dating a declaration.

This study protocol was prepared in accordance with the extension of the Consolidated Standards of Reporting Trials 2010 statement for reporting on cluster randomised trials (online supplemental additional file 6)[31] and the Standard Protocol Items: Recommendations for Interventional Trials 2013 statement for reporting on clinical trial protocols (online supplemental additional file 7).[32]

We will prepare presentations to disseminate the study findings to healthcare stakeholders and patients, and at relevant national and international conferences. We aim to publish the results of the trial in peer-reviewed journals.

Author affiliations
[1]Institute of General Practice, Goethe University Frankfurt, Frankfurt am Main, Germany
[2]Department of Medical Informatics, Biometry and Epidemiology, Ruhr University, Bochum, Germany
[3]Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC), Madrid, Spain
[4]Department of Internal Medicine, Clinic Saarbrücken, Saarbrücken, Germany
[5]Association of Statutory Health Insurance Physicians, Region Westphalia/Lippe, Dortmund, Germany
[6]Center for Health Economics and Health Services Research, University of Wuppertal, Wuppertal, Germany
[7]BARMER, Wuppertal, Germany
[8]Department of Health Economics and Health Care Management. Faculty of Health Science, Bielefeld University, Bielefeld, Germany
[9]PMV Research Group, Faculty of Medicine, University Hospital Cologne, University of Cologne, Cologne, Germany
[10]Institute for Medical Sociology, Health Services Research and Rehabilitation Science, Department of Health Services Research, University of Cologne, Cologne, Germany
[11]RpDoc Solutions GmbH, Saarbrücken, Germany
[12]Department of Rehabilitation Sociology, Faculty of Rehabilitation Sciences, Technical University Dortmund, Dortmund, Germany
[13]Institute for Clinical Pharmacology, Goethe University Frankfurt, Frankfurt am Main, Germany
[14]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
[15]Centre for Research in Evidence-Based Practice (CREBP), Bond University, Robina, Queensland, Australia
[16]Institute of Medical Sociology, Health Services Research and Rehabilitation Science, University of Cologne, Cologne, Germany
[17]Department of General Practice and Family Medicine, Medical Faculty OWL, Bielefeld University, Bielefeld, Germany

Twitter Rafael Perera @rafaoxford and Holger Pfaff @@PfaffHolger

Acknowledgements We would like to thank all practice teams and patients for their participation in the study and also Sandra Rauck and Kiran Chapidi for their contributions as data managers. We appreciate the project management support from BARMER and KVWL. We also thank Phillip Elliott for the language review of the paper.

Collaborators AdAM study group: Julia Jachmich, Eva Leicher, Benjamin Brandt, Johanna Richard, Frank Meyer, Mathias Flume, Thomas Müller, Kiran Chapidi, Robin Brünn, Jale Basten, Karolina Beifuß.

Contributors AIG-G drafted the first version of the manuscript with input from BSM and CM. Critical revision of manuscript for important intellectual content: RK-M, NT and HJT. CM, HJT, FMG, DG, WG, SH, RP, PG, HP, UK, PK-M and PI are responsible for study concept and design. PK-M is the study director. Acquisition of data: BSM, BF, RH, PK-M, TB, LD, TSD, SG, JK-N, AP, UK, SS. Analysis and interpretation of data will be performed by RK-M, JK-N, HJT, BS, PI, SS, UK, AP, WG, CM, NT, IM. PI is responsible for strategic data management. CM and NT are the chief investigators of the study. All authors reviewed the paper and read and approved the final manuscript. CM and NT shared the last authorship.

Funding This study was funded by the Innovation Fund of the German Federal Joint Committee (grant no 01NVF16006).

Disclaimer The funder had no role in the design of the study, or in writing the manuscript.

Competing interests BSM, RK-M, AIG-G, RH, JK-N, PK-M, NT, TB, LD, BS, BF, PI, SS, TSD, AP, IM, UK, HP, WG, FMG, HJT, CM report grants from the German Federal Joint Committee during the conduct of the study. DG reports grants from BARMER during the conduct of the study and family member works for and holds shares of IT company involved in the project. SG works for and holds shares of IT company involved in the project. SH, RP, PG declare that they have no competing interests.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Beate S Müller http://orcid.org/0000-0002-6745-1047
Ana Isabel Gonzalez-Gonzalez http://orcid.org/0000-0002-1707-0596
Rafael Perera http://orcid.org/0000-0003-2418-2091
Paul Glasziou http://orcid.org/0000-0001-7564-073X
Christiane Muth http://orcid.org/0000-0001-8987-182X

REFERENCES

1 Ferner RE, Aronson JK. Communicating information about drug safety. *BMJ* 2006;333:143–5.
2 Weng M-C, Tsai C-F, Sheu K-L, *et al*. The impact of number of drugs prescribed on the risk of potentially inappropriate medication among outpatient older adults with chronic diseases. *QJM* 2013;106:1009–15.
3 Campbell SE, Seymour DG, Primrose WR, *et al*. A multi-centre European study of factors affecting the discharge destination of older people admitted to hospital: analysis of in-hospital data from the ACMEplus project. *Age Ageing* 2005;34:467–75.
4 Hanlon JT, Schmader KE, Ruby CM, *et al*. Suboptimal prescribing in older inpatients and outpatients. *J Am Geriatr Soc* 2001;49:200–9.
5 Thomsen LA, Winterstein AG, Søndergaard B, *et al*. Systematic review of the incidence and characteristics of preventable adverse drug events in ambulatory care. *Ann Pharmacother* 2007;41:1411–26.
6 Rodrigues MCS, Oliveira Cde, de OC. Drug-drug interactions and adverse drug reactions in polypharmacy among older adults: an integrative review. *Rev Lat Am Enfermagem* 2016;24.
7 Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000;356:1255–9.
8 Field TS, Gurwitz JH, Avorn J, *et al*. Risk factors for adverse drug events among nursing home residents. *Arch Intern Med* 2001;161:1629.
9 Lu W-H, Wen Y-W, Chen L-K, *et al*. Effect of polypharmacy, potentially inappropriate medications and anticholinergic burden on clinical outcomes: a retrospective cohort study. *CMAJ* 2015;187:E130–7.
10 Frazier SC. Health outcomes and polypharmacy in elderly individuals. *J Gerontol Nurs* 2005;31:4–9.

11 Franchi C, Marcucci M, Mannucci PM, *et al*. Changes in clinical outcomes for community-dwelling older people exposed to incident chronic polypharmacy: a comparison between 2001 and 2009. *Pharmacoepidemiol Drug Saf* 2016;25:204–11.
12 Lai S-W, Liao K-F, Liao C-C, *et al*. Polypharmacy correlates with increased risk for hip fracture in the elderly: a population-based study. *Medicine* 2010;89:295–9.
13 Sganga F, Landi F, Ruggiero C, *et al*. Polypharmacy and health outcomes among older adults discharged from Hospital: results from the crime study. *Geriatr Gerontol Int* 2015;15:141–6.
14 Crooks J. Rational therapeutics in the elderly. *J Chronic Dis* 1983;36:59–65.
15 Vestal RE. Drug use in the elderly. *Drugs* 1978;16:358–82.
16 Vestal RE. Aging and pharmacology. *Cancer* 1997;80:1302–10.
17 Koper D, Kamenski G, Flamm M, *et al*. Frequency of medication errors in primary care patients with polypharmacy. *Fam Pract* 2013;30:313–9.
18 Panesar SS, deSilva D, Carson-Stevens A, *et al*. How safe is primary care? A systematic review. *BMJ Qual Saf* 2016;25:544–53.
19 Slabaugh SL, Maio V, Templin M, *et al*. Prevalence and risk of polypharmacy among the elderly in an outpatient setting. *Drugs Aging* 2010;27:1019–28.
20 World Health Organization (WHO). *Multimorbidity: technical series on safer primary care*. Geneva, 2016.
21 Meid AD, Quinzler R, Freigofas J, *et al*. Medication underuse in aging outpatients with cardiovascular disease: prevalence, determinants, and outcomes in a prospective cohort study. *PLoS One* 2015;10:e0136339
22 Rankin A, Cadogan CA, Patterson SM, *et al*. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev* 2018;9:CD008165.
23 Christie J. Interventions to improve the appropriate use of polypharmacy for older people: a cochrane review summary. *Int J Nurs Stud* 2019;93:84–6.
24 Muth C, Blom JW, Smith SM. Evidence supporting the best clinical management of patients with multimorbidity and polypharmacy: a systematic guideline review and expert consensus. *J Intern Med* 2019;283:272–88.
25 Bates DW, Kuperman GJ, Wang S, *et al*. Ten commandments for effective clinical decision support: making the practice of evidence-based medicine a reality. *J Am Med Inform Assoc* 2003;10:523–30.
26 Monteiro L, Maricoto T, Solha I, *et al*. Reducing potentially inappropriate prescriptions for older patients using computerized decision support tools: systematic review. *J Med Internet Res* 2019;21:e15385.
27 O'Mahony D, O'Sullivan D, Byrne S, *et al*. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015;44:213–8.
28 World Health Organization (WHO). *ICD-10 transition*. 18. Family practice management, 2011.
29 Quinzler R, Freitag MH, Wiese B, *et al*. A novel superior medication-based chronic disease score predicted all-cause mortality in independent geriatric cohorts. *J Clin Epidemiol* 2019;105:112–24.
30 World Medical Association. World medical association declaration of helsinki. *JAMA* 2013;310:2191.
31 Campbell MK, Piaggio G, Elbourne DR, *et al*. CONSORT 2010 statement: extension to cluster randomised trials. *BMJ* 2012;345:e5661
32 Chan A-W, Tetzlaff JM, Altman DG, *et al*. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
33 Dreischulte T, Donnan P, Grant A, *et al*. Safer prescribing--a trial of education, informatics, and financial incentives. *N Engl J Med* 2016;374:1053–64.
34 Muth C, Harder S, Uhlmann L, *et al*. Pilot study to test the feasibility of a trial design and complex intervention on prioritising MUltimedication in multimorbidity in general practices (PRIMUMpilot). *BMJ Open* 2016;6:e011613.
35 Bergert F, Braun M, Ehrenthal K. *Hausärztliche leitlinie multimedikation empfehlungen zum umgang MIT*, 2016.
36 Muth C, Kirchner H, van den Akker M, *et al*. Current guidelines poorly address multimorbidity: pilot of the interaction matrix method. *J Clin Epidemiol* 2014;67:1242–50.
37 Muth C, Gensichen J, Butzlaff M. *DEGAM leitlinie. NR. 9: herzinsuffizienz*. Düsseldorf: Omikron Publishing, 2006.
38 Renom-Guiteras A, Meyer G, Thürmann PA, a TP. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. *Eur J Clin Pharmacol* 2015;71:861–75.
39 Crediblemeds. Combined list of drugs that prolong QT and/or cause torsades de pointes (TDP), 2014. Available: https://www.crediblemeds.org/

Additional file 1. Brief description of AdAM sub-studies

SUB-STUDY BIELEFELD. HEALTH-ECONOMIC ANALYSIS.

The aim of this sub-study is to estimate the cost-effectiveness of the AdAM intervention compared to usual care.

The economic analysis will be conducted from a third-party payer perspective, which is the perspective of the statutory health insurance funds in Germany. Health effects will be measured by use of the composite endpoint of the clinical study combining hospital admissions and deaths.

The analysis of all reimbursed direct health care costs will be based on health insurance claims data comprising details on physician visits, inpatient hospital stays, pharmaceuticals (prescription medication), outpatient health care services provided by non-physicians and therapeutic appliances, rehabilitation, and sick pay. Arising costs, such as costs of IT-infrastructure, coordination, maintenance, training and fees, will be used to estimate the overall costs of the AdAM intervention. Fees for physicians will be varied in sensitivity analysis.

The cost-effectiveness of the intervention will be measured by the incremental cost-effectiveness ratio (ICER), which is expressed as the ratio of the difference in overall costs between the control and the intervention group and the difference in effects between both groups. For the ICER calculation of the base case, mean values of costs and effects will be used. In sensitivity analysis, also median values will be used.

Further analyses will be based on the composite endpoint's components (hospital admissions and deaths), on life years gained (LYs), and on quality-adjusted life years (QALYs). To determine the LYs, the remaining life expectancy in both the control and intervention group will be estimated using mortality tables. In order to take into account differences in quality of life between ages when calculating QALYs, age-dependent utility values will be obtained from the literature.

All future costs and health effects will be discounted by 3% per year according to recommendations by the German institute for efficiency and quality in health care (IQWiG). In sensitivity analysis, the discount rate will be varied from of 0% to 5%.

SUB-STUDY KÖLN. ANALYSIS OF BARRIERS AND FACILITATORS: QUALITATIVE INTERVIEWS AND FOCUS GROUPS WITH PHYSICIANS.

The aim of this sub-study is to identify factors facilitating or hindering the successful implementation of the intervention from a general practitioner's point of view and evaluate which factors facilitate or hinder the effective performance of systematic medication-checks and optimization. Hereby is expected to get insights how the intervention can be optimized and adapted for general practitioners' high-level acceptance and effectiveness of optimized medication-checks by area-wide implementation.

Therefore a multistage mixed-methods-Approach will be conducted (combination of qualitative and quantitative outcomes) (1).

Level 1: To analyze general practitioners subjectively perceived barriers and resources regarding implementation, guided expert-interviews will be conducted (n= 5-10) (face-to-face-interviews or telephone-interviews) (2,3) to explore the field. Therefore, a convenient sample strategy will be applied. Furthermore, formative evaluation will take part during the trial with two additional time points of qualitative data collection related to relevant emerging topics concerning successful implementation.

Level 2: Results of qualitative data collection will be used for understanding practical orientation patterns of general practitioners (how do they actually use AdAM in real life settings) and their conjunctive experiential space (4). Focus groups with general practitioners of intervention and control group (total, n= 4) will be conducted concerning their experiences and expectations of the project.

Level 3: Results of qualitative data collection will be used to prepare a quantitative general practitioners survey, in which ~~all~~ participating physicians of the intervention group will be asked about barriers and facilitators of the implementation. The survey aims representative detection of general practitioners factors, which facilitate or hinder implementation and identify specific attributes of 'early adapters' and 'late adapters' (5). Quantitative data will be evaluated descriptive and by applying appropriate multiple regression models.

The quality of the qualitative research data collection and analysis in interviews and focus groups is assured by audio recording as well as by transcription according to established standards and by independent coding and subsequent interpretation by a group of researchers. Data analysis will comprise qualitative content analysis according to Kuckartz (6).

Quality assurance concerning the survey conduct is assured by standards of survey development, pretesting, Dillman's Total Design (7) method for increasing response rates and data preparation with the Teleform® software.

SUB-STUDY FRANKFURT. ANALYSIS OF BARRIERS, FACILITATORS AND UNINTENDED CONSEQUENCES: QUALITATIVE INTERVIEWS WITH PATIENTS

The aim of this sub-study is to identify factors facilitating or hindering the successful implementation of the intervention. We especially focus on patient-perceived unintended consequences of the intervention, e.g. fear resulting from the exchange of information between several doctors or resentments towards the implemented technology.

The sub-study starts after the positive ethics vote dedicated to the qualitative study has been received (second vote). Patients who have already received the intervention, can be included in the study (inclusion criterion: invoiced EBM-code). Patients will be recruited by their general practitioners. General practitioners are trustful "gatekeepers" with the potential to motivate patients to participate (8). After written informed consent, contact details will be forwarded to the Institute of General Practice in Frankfurt/Main. A target sample of 20 patients (balanced with regard to sex, age) out of two or more practices will be included in the study.

We will interview the patients via telephone (9); the interviews are expected to take 20-40 minutes each. The interviewer will use a semi-structured interview guide, which will be pilot-tested in three to four think-aloud-interviews beforehand. Interviews will be audio recorded after informed consent and transcribed verbatim according to established standards (10). Data analysis will comprise qualitative content analysis according to Kuckartz (10). Data will be independently coded and subsequently interpreted by two researchers. The strategy of subsumption will be used to develop content categories mixed deductively-inductively. Data will be evaluated supported by software MAXQDA© at Goethe University in the Institute of General Practice in Frankfurt/Main.

ADAM PROCESS EVALUATION

A process evaluation is an essential part of the evaluation of complex medical interventions. The process evaluation in AdAM will study the following aspects:

1) Numbers of patients per practice from the list of potentially eligible patients that participated in AdAM ("reach")
2) Enrolment rate of GPs, general practices and patients measured as the number of GPs, general practices and patients per potentially eligible number of GPs, general practices and patients during the 15 months from baseline minus baseline (T1–T0) ("reach").
3) Number of patients per practice that were not included in the list of potentially eligible patients that participated in AdAM to evaluate the number of patients who benefit from the AdAM service.
4) Quantitative aspects of the intervention: to which extent was the intervention eMMa® applied to patients ("dose")?
    a. Number of GPs and general practices who use eMMa® to print a medication plan 15 months (once a year and more than once a year) from baseline minus baseline (T1–T0).
    b. Number of safety key figures retrievals and use of patient safety examination to ensure the frequency of use of eMMa® safety functionalities (BRAVO quality indicators).
5) Qualitative aspects of the intervention: was the intervention eMMa® applied as planned ("fidelity")?
6) Adaptation of the intervention: which modifications were made to adjust the intervention to heterogeneous processes in participating practices ("tailoring")?

Software log files provided by RpDoc®Solutions GmbH will comprise the data needed for analyses. Pseudonyms will be used to prevent identification of individual patients, practices or doctors.

Further details of the process evaluation (detailed research questions, MDS) will be provided a priori to the planned analyses.

ADAM SUSTAINABILITY ASSESSMENT

A fading effect over time in interventions for the improvement of drug management has been mentioned in the literature (11). This sustainability assessment aims to analyze such temporary effects. The goal is to determine if improvements in the prescription of drugs due to eMMa® can still be found after more than five quartiles. Therefore, it is necessary for both the intervention group and the control group to receive the intervention, i.e. eMMa®.

The sustainability assessment is meant to provide insights on the planned rollout on larger groups. Therefore, it is necessary for the control group to receive the full intervention.

Any further details will be pre-specified in a separate protocol.

SUB-STUDY WUPPERTAL: QCAS TO EXPLORE THE RELATIONSHIP BETWEEN ORGANIZATIONAL CONTEXT, IMPLEMENTATION PROCESS AND QUALITY OF CARE

The aim of this sub-study is to examine the process of effectiveness development, the interaction among key drivers (configurations of success) and to investigate, how these key drivers influence effect sustainability. The analyses of this sub-study will be based on practices of the intervention group of the parallel cluster-randomised controlled trial (c-RCT) and those practices of the control group who joined the intervention mode 15 months after their recruitment. We will include all control group practices who change intervention status at least until 30/06/2020.

QCAs will be based on a conceptual model comprising contextual and implementation process factors affecting intervention's effectiveness. Research suggests that attributes characterising the organisational context are important for the development of habitual behaviour and the successful adoption of interventions (12). In addition, contemporary definitions of organisations have evolved from a closed-system perspective (organisations = isolated systems with no interaction with their environment) to an open-system perspective. Therefore, organisational attributes will be defined on three distinct levels of analysis: 1) the behaviour of individuals, 2) the structural features and 3) the organisation viewed as an entity operating in a larger system of relations (13).

Analytic methods

In a first step, fuzzy set qualitative comparative analysis will be used to identify pathways – that is, different combinations of organisational attributes and implementation process characteristics – associated with:

1. sites' success in attaining a relative risk reduction in the primary end point at the end of the c-RCT (change is measured in comparison to the control groups' results) – QCA 1,
2. short term effects (change of secondary endpoints after the first five months of intervention) – QCA 2.

In a second step, the findings of the first QCA will be integrated in a multilevel model (two-level HML) in which the cross-level interactions of the pathways will be investigated and mechanisms suited for reaching sustainability at the end of a three month follow-up phase will be explored.

To prepare results of the first QCA for use in HLM, a categorisation of each study site as a member of one of the pathways is planned. Only those practices will be included in the multilevel model that are member of a configuration sufficient for outcome and part of c-RCT's intervention group. To explore mechanisms suited for a sustainable intervention effect, the two-level HLM will be estimated with the pathways (configurations) at the macro level. At the micro level a variable, which measures the stability of the attained performance level (dichotomous definition: "1" if there is no increase in all-causes hospital admissions and all-causes deaths per practice over the follow-up phase, otherwise "0") will be included. As explanatory variables the four constructs of the normalisation process theory (NPT; coherence, cognitive participation, collective action, reflexive monitoring) will be considered. This construct will be measured at the beginning of the follow-up phase and by applying the instrument NoMAD (14). They will describe physicians' views about how an intervention impacts on their work, and their expectations about whether it could become a routine part of their work.

Site sampling and data source:

The first QCA and the multilevel model will include only practices of the intervention group. The second QCA will use practices of the control group as well, after this group has joined the intervention mode.

Parameters corresponding to factors in the conceptual model will be derived from a survey, which is organised in two waves (first in 2019, second in 2020). The outcome measure will be based on secondary data (claims data). In addition, structural data of the practices (e.g. practice infrastructure, patient structure) and use of support will be obtained from other project partners (e.g. by extracting information out of CDSS log files).

REFERENCES

1. Mayring P. Evidenztriangulation in der Gesundheitsforschung. KZfSS Kölner Zeitschrift für Soziologie und Sozialpsychologie. 2017 Oct 10;69(S2):415–34.
2. Bogner A, Littig B, Menz W. Experteninterviews. Theorien, Methoden, Anwendungsfelder. 3., grundlegend überarbeitete Auflage. Wiesbaden: VS Verlag für Sozialwissenschaft; 2009.
3. Christmann G. Telefonische Experteninterviews. In: Alexander Bogner, Beate Littig und Wolfgang Menz (Hg): Experteninterviews Theorien, Methoden, Anwendungsfelder 3, grundlegend überarbeitete Auflage. Wiesbaden: VS Verlag für Sozialwissenschaften; 2009.
4. Bohnsack R. Dokumentarische Methode und sozialwissenschaftliche Hermeneutik. Zeitschrift für Erziehungswiss. 2003;6(4):550–70.
5. Rogers EM. Diffusion of preventive innovations. Addict Behav. 2002 Nov;27(6):989–93.
6. Kuckartz U. Einführung in die computergestützte Analyse qualitativer Daten. Wiesbaden: VS Verlag für Sozialwissenschaften; 2007.
7. Dillman DA, Smmyth JS, Christian LM. Internet, phone, mail, and mixed-mode surveys: the tailored design method. Wiley; 2014. 528 p.
8. Helfferich F. Die Qualität qualitativer Daten. Manual für die Durchführung qualitativer Interviews, 3. Überarbeitete Auflage. Wiesbaden: GWV Fachverlage GmbH; 2009.
9. Flick U. Leitfaden-Interviews. In: Qualitative Sozialforschung Eine Einführung. 7th ed. Reinbeck bei Hamburg: Rowohlt; 2007. p. 194–226.
10. Kuckartz U. Qualitative Inhaltsanalyse. Methoden, Praxis, Computerunterstützung. Weinheim: Beltz Juventa; 2012.
11. Avery AJ, Rodgers S, Cantrill JA, Armstrong S, Cresswell K, Eden M, et al. A pharmacist-led information technology intervention for medication errors (PINCER): a multicentre, cluster randomised, controlled trial and cost-effectiveness analysis. Lancet [Internet]. 2012 Apr;379(9823):1310–9. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0140673611618175
12. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci. 2009 Dec 7;4(1):50.
13. Hogg W, Rowan M, Russell G, Geneau R, Muldoon L. Framework for primary care organizations: the importance of a structural domain. Int J Qual Heal Care. 2008 Oct;20(5):308–13.
14. Finch T, Girling M, May C, Mair F, Murray E, Treweek S, et al. Nomad: Implementation measure based on Normalization Process Theory [Internet]. 2015 [cited 2018 Jan 25]. Available from: http://www.normalizationprocess.org/

AdAM Ein Projekt von BARMER und KVWL

Patient information

Application of an electronic medication management support system – AdAM

Dear patient,

Nowadays effective medications are available for the treatment of many illnesses, and it is sometimes necessary that you take a number of different drugs. The aim of the AdAM project is to help ensure that your drugs are carefully selected to avoid unwanted interactions when you take them.

In the following pages, we will explain the project to you and request that you agree to take part in it. The project will be conducted in Westphalia-Lippe and will be scientifically evaluated.

What is the aim of the project?

The BARMER health insurance fund and the Westphalia-Lippe Association of Statutory Health Insurance (SHI) Physicians intend that the AdAM project should further improve the safety of patients taking a number of medications at the same time, and help doctors in the treatment of their patients.

What is new about this project is that your family practitioner will be able to retrieve electronic information from the BARMER database. With the help of these data, participating doctors will gain a more comprehensive overview of all their patients' treatments and prescriptions. Specifically, your family practitioner can access information on the medications, remedies and aids that you have been prescribed in the last 36 months, as well as the diagnoses and treatments that have been documented in the system, including those by other doctors.

All this information will make it easier to check your drug therapy for possible interactions and intolerances. Additionally, you will receive a medication plan with the names of your medications, dosage information, and further easy-to-understand information on taking your drugs.

In order that doctors can call up the required data, every participating practice is electronically linked to an assigned BARMER computer via the Association of SHI Physicians (gkvi, based in Wuppertal, www.gkvi.de).

Who is eligible to participate in the project?

All patients insured by BARMER may participate in the project and receive treatment from one of the participating family practitioners. To be eligible for participation, patients must be taking three prescription medications.

How and what will be scientifically evaluated?

On the one hand, the project will evaluate whether the intervention has enabled hospitalization to be avoided and whether it has led to any changes in drug therapies (project phase 1). On the other hand, the project will check whether these changes have been lasting (project phase 2).

As the first phase of the project is a so-called cluster-randomized study, only half of the participating doctors and their patients may participate in the intervention. It is important to separate the doctors into an intervention group and a control group to determine whether the project has any influence on the success of the therapy. In the second phase of the project, the investigation will aim to determine whether any changes are lasting. In this phase, which will begin after 15 months, doctors in the control group and their patients may also participate in the project intervention.

What is the actual project procedure?

After your doctor has provided you with detailed information and you have read this patient information leaflet, you can provide your written agreement to participate. Subsequently, your family practitioner will immediately be able to retrieve and use data on your treatments that are stored in the BARMER computer. This will be made possible using a particularly secure connection between the family practice and the BARMER computer via the Westphalia-Lippe Association of SHI Physicians (KVWL, based in Dortmund).

The data stored in the BARMER computer and the current status of your treatment will then be compared and updated on the basis of a personal consultation with your doctor in the family practice. After the consultation, the family practitioner will use a computer program that has been specially developed for the project to check your drug therapy for any unwanted interactions.

Should it be necessary, the doctor will contact medical specialists that are treating you and agree on changes to your medication. Afterwards, patients will receive a medication plan that has been updated according to your needs, and which includes all important information.

Will my participation in the project cost anything?

Participation in the project is free of charge for patients.

Can I end my participation in the project prematurely?

The agreement to participate can be withdrawn at any time without providing reasons for doing so, and will not have any negative effects on your medical treatment. It is simply necessary to state that you wish to cancel your participation in written form and send the cancellation letter to BARMER at the following address:

BARMER, Subject: AdAM project, Lichtscheider Str. 89, 42285 Wuppertal

What will happen to my data?

The family practitioner is the only person to have complete access to patients' treatment data stored at BARMER, and you have signed the agreement to participate only with reference to your family practitioner.

The data used in the project will be transmitted and stored in encrypted form. Family practitioners can only make changes to data they have entered into the database during the course of the project.

Your family practice will transmit your signed declaration of consent and agreement to participate to the Westphalia-Lippe Association of SHI Physicians where it will be stored electronically. The signed document will then be forwarded to BARMER. All participating patients will be registered with the Westphalia-Lippe Association of SHI Physicians and the BARMER insurance fund for the purpose of carrying out the project, as well as healthcare accounting.

Your family practitioner will be permitted to access all the medical data stored at BARMER for a period of up to three years. The data will include an overview of all the doctors that have treated you, including their documented diagnoses, all prescription invoices and information on hospitalization (inpatient diagnoses, dates of admission and discharge, name of the hospital). You have the right to see, correct and delete data that has been entered into the database by the doctor, as well as the right to object to specific data and the right to data portability.

The data on participating patients will be made available to the universities that have been commissioned to conduct the scientific evaluation in pseudonymized form. Pseudonymized means that names and other personally identifiable information (e.g., social insurance number) will be replaced with artificial identifiers, so that research scientists are unable to recognize the specific person that is referred to.

Should a participating patient file an objection, or wish to discontinue participation in the project, or if the contract with the Westphalia-Lippe Association of SHI Physicians is cancelled, all data that have been collected as part of the project will, on receipt of the corresponding notification, be deleted.

Who do I contact if I have any further questions?

If you have any further questions, please call the toll-free telephone number 0800 333 004 327 331 from a German fixed or mobile phone network.

Participating doctor's personal seal

DECLARATION OF CONSENT AND AGREEMENT TO PARTICIPATE IN THE PROJECT

Application of an electronic medication management support system

The Westphalia-Lippe Association of Statutory Health Insurance Physicians (KVWL) and the BARMER health insurance fund have signed a contract for the application of an electronic medication management support system. In abbreviated form, the project is also known as **AdAM**.

Declaration of consent and agreement to participate

I have been extensively and comprehensively informed about the nature, significance and implications of the AdAM project. I have read and understood the text of the patient information leaflet. I had the opportunity to discuss the implementation of the project with my family practitioner. All my questions were answered to my satisfaction.

I agree to permit my doctor to retrieve data on my invoiced treatments and drug prescriptions from all physicians that have treated me over the past 36 months on an ongoing basis. I would like my doctor to comprehensively check my medication on the basis of a cross-physician overview of all my treatment data. My family practitioner will also receive information on my hospitalizations, including diagnoses documented by hospitals, as well as, for example, invoiced prescriptions for remedies and medical aids, and nursing care. I am pleased that my doctor will be supported by BARMER in my medication and care management.

If necessary, I consent to my doctor contacting my other medical specialists in order to discuss my drug therapy.

My participation in this project is voluntary. Participation under the conditions of the contract begins when I sign this declaration of consent. My participation ends when I revoke or cancel this declaration, when the contract expires, or if I am no longer insured by BARMER.

I also agree that the Westphalia-Lippe Association of Statutory Health Insurance Physicians (KVWL, based in Dortmund) and BARMER should collect, process and otherwise use my data in order to carry out this project, as well as for healthcare accounting. This agreement to participate will be electronically recorded at KVWL and transmitted to BARMER. KVWL and BARMER will treat my data confidentially and in compliance with prevailing data protection regulations.

Cancellation policy

I can cancel my participation within two weeks of signing an agreement to participate without providing reasons. To meet the deadline, it is sufficient that notice of cancellation is sent to BARMER in due time. After the deadline has expired, it remains possible to cancel participation in the project. In order to provide notice or cancel, a notice of cancellation should be sent in written form to the following address:

BARMER, Subject: Project AdAM, Lichtscheider Str. 89, 42285 Wuppertal.

Krankenkasse bzw. Kostenträger BARMER		
Name, Vorname des Versicherten <FV31901_Komplettname> <FV31901_Vorname> <FV31901_Strasse> >FV31901_Hausnr> <FV31901_PLZ> <FV31901_Ort>		geb. am <FV31901_Gebdatum>
Kostenträgerkennung 104940005	Versicherten-Nr. <FV31901_KVNR >	Status
Betriebsstätten-Nr. <FV31901_BSNR>	Arzt-Nr. <FV31901_LELANR>	Datum

QR-Code

18mm x 18mm

Declaration of consent and agreement to participate

DECLARATION OF CONSENT AND AGREEMENT TO PARTICIPATE IN THE PROJECT:

Application of an electronic medication management support system

I agree to participate in the project for the application of drug therapy and care management (AdAM).

I have received one copy each of the patient information leaflet and the declaration of consent. A further copy will remain in the practice and the signed original will be sent by mail to the Association of Statutory Health Insurance Physicians (KVWL, Dortmund), where it will be electronically registered and forwarded to BARMER.

Date (DD. MM.YYYY) Signature of patient or legal representative

Consent that data may be used for the purpose of scientific evaluation and monitoring

I further agree that, in pseudonymized form and in compliance with prevailing legal requirements, my medical treatment and prescription data may be used for the purpose of scientifically evaluating the cost effectiveness, efficiency and quality of treatment/care management. The scientific evaluation will be conducted by research staff at the participating universities in the German states of North Rhine-Westphalia and Hesse. Pseudonymization means that my name and other identifiers (e.g. social insurance number) will be replaced by labels that rule out the identification of my person.

Date (DD.MM.YYYY) Signature of patient or legal representative

The physician will mail the original declaration of consent to:

KVWL, Projekt AdAM, Robert-Schimrigk-Str. 4-6, 44141 Dortmund.

A copy will also be provided to the patient, and a further copy included in the patient's records at the practice.

Additional file 3. RpDoc® medical database

Screening for and assessment of drug interactions

Goal setting

The medical-scientific editorial team of RpDoc® Solutions GmbH identifies drug interactions by continuously monitoring medical-scientific publications and the notifications of national and international regulatory authorities. A structured process is then employed to systematically analyze and assess them. To help doctors and pharmacists analyze and evaluate drug therapies, the updated knowledge of management options concerning clinically relevant interactions is then summarized and the interactions and management options, along with references, entered into the RpDoc® medical database.

In addition, the RpDoc® medical database contains recommendations made to avoid specific drug combinations that may result from the parallel application of guidelines for individual diseases in patients with multimorbidity. These recommendations have been unanimously agreed upon by medical and pharmaceutical societies and are published as S2K Guidelines by the AWMF Working Group of Scientific Medical Societies.

The basic principles of screening for and evaluating interactions for the RpDoc® medical databases are presented below.

Screening for interactions

The medical-scientific editorial team of RpDoc® Solutions GmbH monitors more than 8,000 peer-reviewed scientific journals listed in the EMBASE or the PUBMED database every week. Risk warnings issued by American and European regulatory authorities for medicinal products, the FDA and EMA, as well as by the German Federal authorities responsible for pharmaceuticals, the Federal Institute for Drugs and Medical Devices (BfArM), and the Paul-Ehrlich Institute, are also monitored weekly. Risk warnings issued by the Drug Commission of the German Medical Association (AkdÄ) and the Drug Commission of German Pharmacists (AMK) are also taken into account.

Assessment of causality

The WHO UMC algorithm is used to evaluate the causality of adverse drug reactions and the information entered into the RpDoc® medical database.

The various methodological approaches available to categorize the causality of adverse drug reactions were compared in a review published in 2018[1]. The WHO algorithm (WHO-UMC) proved to be the most suitable for assessing the causality of adverse drug reactions resulting from drug interactions. It was developed for the International Drug Monitoring Program by the WHO, in collaboration with national pharmacovigilance centers, and is also suitable for the assessment of warning signals stemming from case reports [2]. In contrast to the Naranjo algorithm, WHO-UMC is also suitable for assessing organ toxicity, side effects of overdoses, and drug interactions [3, 4].

DIPS (Drug Interaction Probability Scale) criteria were used to evaluate case descriptions of drug interactions [5].

Assessment of quality of evidence

The evaluation of quality of evidence is based on the GRADE system (Grading of recommendations Assessment, Development and Evaluation) [6]. In evidence evaluations, prospective randomized studies and meta-analyzes are generally assumed to provide high quality evidence. However, indications of adverse drug interactions are often found in case reports and non-randomized studies. Such warnings as those found in Dear Doctor letters from pharmaceutical manufacturers and drug safety mails from the Drug Commission of the German Medical Association can nevertheless be plausible and justify strong recommendations on how to avoid a specific risk.

In the absence of randomized studies, GRADE can still be used. The instrument of “Good Practice Statements" is suitable for situations in which no prospective randomized studies exist, but convincing indirect evidence is available [7]. Good practice statements can justify strong recommendations even if no randomized studies exist, as long as indirect evidence unequivocally supports the recommendation, and other criteria are met [7]. In this case, different sources of evidence can be informally linked (linked evidence) to one another in order to provide information on net benefit [7].

An example of an evaluation of clinical relevance

For liability reasons, pharmaceutical manufacturers provide information on every conceivable risk associated with the use of their drugs, both individually and in combination with other medications, regardless of clinical relevance. When analyzing a drug therapy, consideration of these risk warnings will result in consideration of a high proportion of irrelevant warnings ("alert overkill") [8]. In order to achieve practical relevance, it is necessary to limit warnings to those that are clinically relevant, i.e. to warnings that should be considered when making therapy decisions [9, 10]. The resulting difference is illustrated in the following example:

Product information (Section 4.5) on siponimod (Mayzent) notes that siponimod should not be administered in combination with medicines that “prolong the QT interval". It is only logical that this contraindication is consistently found in databases that contain product information, e.g. in the IBM Micormedex database (classified as "major" = red).

Studies have been submitted by the pharmaceutical company for approval and are available in the European Product Assessment Report of the EMA. These clearly show that siponimod does not increase the QT interval: “A thorough QT study was conducted (study A2118). No effect of siponimod on the QTc interval was detected. ... metabolites are not expected to have significant effects on the QTc interval. "(EMA / CHMP / 652767/2019).

However, the studies also show that siponimod lowers the heart rate. A reduction in heart rate extends the intervals measured by ECGs, including the QT interval, but not the frequency-corrected QT interval that determines the risk of sudden cardiac death. The RpDoc® medical database therefore includes no warning against administering siponimod at the same time as QT interval prolonging drugs, but rather against drugs that may result in additive heart rate reduction.

Design of the recommendations

The design of recommendations has a significant influence on their applicability and effectiveness in practice. In order to facilitate the implementation of recommendations, management options aimed at minimizing risks should be provided in addition to descriptions of avoidable risks [11]. When a warning has high specificity, e.g. because it names particularly affected patient groups or dosages, its effectiveness is increased [10].

When formulating recommendations for action, the recommendations developed by a group of experts on the content of interaction warnings are taken into account [12]. In addition to information on the unwanted effects of a specific drug combination, information on predisposing and risk-minimizing factors, the incidence of adverse effects, and the level of evidence concerning the risk of interaction, are also provided. Pharmacological plausibility and the mechanism of interaction are presented in addition to management options. In particular, references are made to equivalent therapeutic alternatives, as well as recommended surveillance measures in case the drug combination is maintained.

Recommendations for action on drug therapies in multimorbidity

There are guidelines for the evidence-based treatment of numerous diseases, but the parallel application of guidelines for each individual disease can, in multimorbidity, lead to unfavorable and risky drug combinations [13].

To resolve these therapeutic conflicts, medical and pharmaceutical scientific societies develop recommendations for action that the AWMF, with the support of the AdAM and TOP innovation fund projects, publishes in S2K Guidelines. RpDoc® Solutions GmbH is involved in both these innovation fund projects as a technology partner, and recommendations developed for drug therapies in multimorbidity are continuously updated in the RpDoc® medical database.

For an overview of the AdAM and TOP projects, please see the brief summary provided by the joint federal committee (https://innovationsfonds.g-ba.de/).

References:

1. Behera, S.K., et al., Comparison of different methods for causality assessment of adverse drug reactions. Int J Clin Pharm, 2018. 40(4): p. 903-910.
2. Meyboom, R.H., et al., Causal or casual? The role of causality assessment in pharmacovigilance. Drug Saf, 1997. 17(6): p. 374-89.
3. Agbabiaka, T.B., J. Savovic, and E. Ernst, Methods for causality assessment of adverse drug reactions: a systematic review. Drug Saf, 2008. 31(1): p. 21-37.
4. Thaker, S.J., et al., Evaluation of inter-rater agreement between three causality assessment methods used in pharmacovigilance. J Pharmacol Pharmacother, 2016. 7(1): p. 31-3.
5. Horn, J.R., P.D. Hansten, and L.N. Chan, Proposal for a new tool to evaluate drug interaction cases. Ann Pharmacother, 2007. 41(4): p. 674-80.
6. Guyatt, G., et al., GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. Journal of Clinical Epidemiology, 2011. 64(4): p. 383-394.
7. Guyatt, G.H., et al., Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. Journal of Clinical Epidemiology, 2016. 80: p. 3-7.
8. Glassman, P.A., et al., Improving recognition of drug interactions: benefits and barriers to using automated drug alerts. Med. Care, 2002. 40(12): p. 1161-1171.

9. Wright, A., et al., Reduced Effectiveness of Interruptive Drug-Drug Interaction Alerts after Conversion to a Commercial Electronic Health Record. J Gen Intern Med, 2018.
10. Heringa, M., et al., Better specification of triggers to reduce the number of drug interaction alerts in primary care. Int J Med Inform, 2018. 109: p. 96-102.
11. Seidling, H.M., et al., Factors influencing alert acceptance: a novel approach for predicting the success of clinical decision support. J Am Med Inform Assoc, 2011. 18(4): p. 479-84.
12. Floor-Schreudering, A., et al., Checklist for standardized reporting of drug-drug interaction management guidelines. Eur J Clin Pharmacol, 2014. 70(3): p. 313-8.
13. Dumbreck, S., et al., Drug-disease and drug-drug interactions: systematic examination of recommendations in 12 UK national clinical guidelines. BMJ, 2015. 350: p. h949.

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	1, 11	
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	10,11	
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	16	
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	16, 17	
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	17	
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	16, 17	
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	16, 17	

TIDieR checklist

	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	16	_____
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	N/A	_____
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	N/A	_____
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	11	_____
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	N/A	_____

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

TIDieR checklist

Additional file 5. Specifications related to the secondary outcome measures

Each of the condition listed (•) must be met for the respective secondary outcome to be fulfilled.

SOpim-1:

- Diagnosed with any of the following ICD-10: K20-21, K25-28
- Prescribed ATC M01A (except M01AB55 and M01AE52)
- Not prescribed ATC A02B

SOpim-2:

- Age 65+
- Prescribed ATC M01A (except M01AB55 and M01AE52)
- Not prescribed ATC A02B

SOpim-3

- Prescribed ATC B01AC
- Prescribed ATC M01A (except M01AB55 and M01AE52)
- Not prescribed ATC A02B

SOpim-4

- Prescribed either ATC B01AC34 or a combination of ATC B01AC06 with any of the following

ATC: B01AC04, B01AC24, B01AC22

- Not prescribed ATC A02B

SOpim-5

- Prescribed any of the following ATC: B01AA, B01AE, B01AF
- Prescribed ATC M01A (except M01AB55 and M01AE52)
- Not prescribed ATC A02B

SOpim-6

- Prescribed ATC B01AA

- Prescribed ATC B01AC
- Not prescribed ATC A02B

SOpim-7

- Prescribed any of the following ATC: G04BX18, N06AB, N06AX16, N06AX17, N06AX21
- Prescribed ATC M01A (except M01AB55 and M01AE52)
- Not prescribed ATC A02B

SOpim-8

- Prescribed any of the following ATC: H02AB, H02BX
- Prescribed ATC M01A (except M01AB55 and M01AE52)
- Not prescribed ATC A02B

SOpim-9

- Prescribed ATC C09
- Prescribed ATC M01

SOpim-10

- Prescribed any of the following ATC: C03AA, C03BA, C03CA, C03D, C03E
- Prescribed ATC M01A

SOpim-11

- Diagnosed with ICD-10 I50
- Prescribed ATC M01A

SOpim-12

- Diagnosed with ICD-10 I50
- Prescribed ATC N06AA

SOpim-13

- Prescribed any of the following ATC: C03D, C09
- Prescribed ATC A12BA

SOpim-14

• Diagnosed with ICD-10 I50

• Prescribed any of the following ATC: C07AA, C07BA, C07DA, S01ED (except S01ED02)

SOpim-15

• Age 65+

• Prescribed any of the following ATC: A03FA03, A04AA01, B01AC23, C01BC04, C01BD01, C01BD07, C07AA07, C08DA81, H01BA04, L01XE12, L01XX35, N05AA02, N05AC02, N05AD01, N05AD08, N05AF03, N05AG02, N05AL01, N06AB04, N06AB10, N06DA02, N07BC02, P01BA01, P01BA02

SOpim-16

• Any of the following:

1.

• Prescribed any two of the following ATC: A03FA03, A04AA01, B01AC23, C01BC04, C01BD01, C01BD07, C07AA07, C08DA81, H01BA04, L01XE12, L01XX35, N05AA02, N05AC02, N05AD01, N05AD08, N05AF03, N05AG02, N05AL01, N06AB04, N06AB10, N06DA02, N07BC02, P01BA01, P01BA02

2.

• Prescribed any of the following ATC: C01BC04, N05AC02, N06DA02, A04AA01, N05AD01, N06AB04, N06AB10

• Prescribed any of the following ATC: A08AA62, N06AX12, N07BA02, H05BX01, N06AB03, N06AB05, C08DA81

3.

• Prescribed any of the following ATC: A04AA01, N05AD01, N06AB04, N06AB10, A03FA03, B01AC23, C08DA81, N05AG02, N07BC02

• Prescribed any of the following ATC: A02BD04, A02BD05, J01FA09, J05AE02, J02AC02, J02AB02, J05AE03, J05AP53, J05AR10, J05AE01, L01XX47, L01XE42, J01FA15

4.

• Diagnosed with any of the following ICD-10: I50, R00.1, I49.5, I49.8

• Prescribed any of the following ATC: A03FA03, A04AA01, B01AC23, C01BC04, C01BD01, C01BD07, C07AA07, C08DA81, H01BA04, L01XE12, L01XX35, N05AA02, N05AC02, N05AD01, N05AD08, N05AF03, N05AG02, N05AL01, N06AB04, N06AB10, N06DA02, N07BC02, P01BA01, P01BA02

SOpim-17

• Prescribed ATC C01AA

• Prescribed any of the following ATC: C03AA, C03BA, C03CA, C07B, C07C, C08GA23, C09BA, C09BX01, C09BX03, C09DA, C09DX01, C09DX03, C09DX06, C09DX07, C09XA52, C09XA54

• Not prescribed ATC A12BA

SOpim-18

• Age 65+

• Prescribed any of the following ATC: A03CA02, C04AD03, C04AE01, C04AE02, C04AE04, C04AE54, C04AX01, C04AX07, C04AX10, C04AX17, C04AX20, C04AX21, C05CA05, C05CA07, C05CA51, C05CA54, M03BA02, M03BA03, M03BC01, M03BX01, M03BX02, M03BX07, M03BX08, N02AB02, N03AE01, N04AA01, N04AA02, N04AA12, N04AC01, N04BB01, N04BC08, N05AA01, N05AA02, N05AA04, N05BA05, N05AB02, N05AB03, N05AB04, N05AC01, N05AC02, N05AD01, N05AD08, N05AE03, N05AF05, N05AG02, N05AH02, N05AH03, N05BA01, N05BA02, N05BA03, N05BA04, N05BA05, N05BA06, N05BA08, N05BA09, N05BA11, N05BA12, N05BA13, N05BA16, N05BA18, N05BA21, N05CD01, N05CD02, N05CD03, N05CD04, N05CD05, N05CD06, N05CD07, N05CD08, N05CD09, N05CD10, N05CD11, N05CF01, N05CF02, N05CF03, N06AA01, N06AA02, N06AA04, N06AA06, N06AA09, N06AA10, N06AA12, N06AA21, N06AB05, N06AB08, N06AX16, N06DX02

SOpim-19

- Diagnosed with any of the following ICD-10: G20-23
- Prescribed any of the following ATC: A03CA02, C04AD03, C04AE01, C04AE02, C04AE04, C04AE54, C04AX01, C04AX07, C04AX10, C04AX17, C04AX20, C04AX21, C05CA05, C05CA07, C05CA51, C05CA54, M03BA02, M03BA03, M03BC01, M03BX01, M03BX02, M03BX07, M03BX08, N02AB02, N03AE01, N04AA01, N04AA02, N04AA12, N04AC01, N04BB01, N04BC08, N05AA01, N05AA02, N05AA04, N05BA05, N05AB02, N05AB03, N05AB04, N05AC01, N05AC02, N05AD01, N05AD08, N05AE03, N05AF05, N05AG02, N05AH02, N05AH03, N05BA01, N05BA02, N05BA03, N05BA04, N05BA05, N05BA06, N05BA08, N05BA09, N05BA11, N05BA12, N05BA13, N05BA16, N05BA18, N05BA21, N05CD01, N05CD02, N05CD03, N05CD04, N05CD05, N05CD06, N05CD07, N05CD08, N05CD09, N05CD10, N05CD11, N05CF01, N05CF02, N05CF03, N06AA01, N06AA02, N06AA04, N06AA06, N06AA09, N06AA10, N06AA12, N06AA21, N06AB05, N06AB08, N06AX16, N06DX02

SOum-1

- Diagnosed with ICD-10 I48
- Not prescribed any of the following ATC: B01AA, B01AE, B01AF

SOum-2

- Diagnosed with any of the following ICD-10: I20-I22, I24-25, I63-66, I69, I70-72, I74
- Not prescribed any of the following ATC: B01AC04, B01AC06, B01AC22, B01AC24, B01AC34, B01AC36

SOum-3

- Diagnosed with any of the following ICD-10: I20-25
- Not prescribed ATC C07

SOum-4

- Prescribed any of the following ATC: L01BA01, L04AX03, M01CX01

- Not prescribed ATC B03BB

SOum-5

- Prescribed ATC N02A (except N02AA55 and N02AX51)
- Not prescribed any of the following ATC: A06AB, A06AD, A06AH

SOum-6

- Diagnosed with any of the following ICD-10: I20-25, I50
- Not prescribed ATC C09 (except C09X)

SOum-7

- Diagnosed with ICD-10 I50
- Not prescribed any of the following ATC: C07AB02, C07AB07, C07AB12, C07AG02, C07BB02, C07BB07, C07BB12, C07BB22, C07BB27, C07BB52, C07BG02 C07CB02, C07CB22, C07FB02, C07FB07, C07FB12, C07FB13, C07FB22, C07FX03, C07FX04, C07FX05, C07FX06

SOum-8

- Diagnosed with any of the following ICD-10: J44-45
- Not prescribed any of the following ATC: R03AC, R03AK, R03AL, R03BB

SOum-9

- Diagnosed with any of the following ICD-10: J44-45
- Not prescribed any of the following ATC: R03AK (except R03AK01, R03AK02, R03AK03, R03AK04 and R03AK05), R03AL08, R03AL09, R03BA

SOum-10

- Diagnosed with any of the following ICD-10: E10-11, E14
- Not prescribed ATC C09 (except C09X)

Additional file 6. CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	6
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	9
	2b	Specific objectives or hypotheses	Whether objectives pertain to the cluster level, the individual participant level or both	10
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	11
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		NA
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	11
	4b	Settings and locations where the data were collected		11
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	14
Outcomes	6a	Completely defined pre-specified primary and	Whether outcome measures pertain to the cluster level, the	16

		secondary outcome measures, including how and when they were assessed	individual participant level or both	
	6b	Any changes to trial outcomes after the trial commenced, with reasons		NA
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	21
	7b	When applicable, explanation of any interim analyses and stopping guidelines		20
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		13
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	13
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	13
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	12-14
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	12-14

	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	12-14
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	12-14
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		14
	11b	If relevant, description of the similarity of interventions		NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	21
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		NA
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	NA
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	NA
Recruitment	14a	Dates defining the periods of recruitment and follow-up		NA

	14b	Why the trial ended or was stopped		NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	NA
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	NA
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	NA
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		NA
Discussion				25
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		25
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	NA
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and		NA

		considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	7
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	26

** Note: page numbers optional depending on journal requirements*

REFERENCES

1 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283

2 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

3 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

Additional file 7. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	8
	2b	All items from the World Health Organization Trial Registration Data Set	8
Protocol version	3	Date and version identifier	34
Funding	4	Sources and types of financial, material, and other support	34
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	33
	5b	Name and contact information for the trial sponsor	33-34
	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	34
	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)	33
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	11-13
	6b	Explanation for choice of comparators	11-13
Objectives	7	Specific objectives or hypotheses	12-13
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)	13-14
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	13-14
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)	13-14
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	17-19 Additional file 3
	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)	23
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	17-19
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	17-19
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	19-21

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)	16 Figure 2
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	24
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	24
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	16, 24-25
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	16, 24-25
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16, 24-25
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			

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	22-24
	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	22-24
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	22-24
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	24-25
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	24-25
	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)	24-25
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	21-22
	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	21-22

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	21-22
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	21-22
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	27
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)	27
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17-19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	17-19
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	22
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	34
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	34
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	21-22

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	28
	31b	Authorship eligibility guidelines and any intended use of professional writers	nr
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	34
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file 5
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	nr

*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.