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TITLE

Implementation of an electronic medication management support system in hospitalised polypharmacy patients: study protocol of a stepped-wedge cluster-randomised controlled trial (TOP study)

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ABSTRACT

Introduction: Polypharmacy is associated with an increased risk of adverse patient outcomes especially in the context of inpatient care. To enhance the appropriateness of medication therapy management for patients during hospital stays, computerised interventions have shown promise with regard to patient safety. This study assesses whether the implementation of a clinical decision support system will optimise the process of inpatient medication therapy to prevent inappropriate medication use and thus promote patient safety.

Methods and analysis: The intervention will be evaluated in a prospective, cluster-randomised controlled trial using a stepped-wedge design. The study will be conducted in 12 hospitals across Germany over a total period of 33 months. Patients will be treated according to the group status of the hospital and receive either standard care or the TOP intervention. The primary outcome is the combined endpoint of all-cause mortality and all-cause hospitalisation. Secondary endpoints are e.g. inappropriate prescriptions, utilisation of different health services, cost-effectiveness, as well as patient-reported outcome measures. Parameters describing the attitudes of patients and healthcare professionals towards the intervention and organisational change processes will be collected as part of the process evaluation. The primary endpoint will be evaluated using claims data from participating statutory health insurances at the population level. There are multiple secondary endpoints with data linkage of primary and secondary data at study participant level. Statistical analysis will make use of (generalised) linear mixed models or generalised estimating equations, taking account of independent covariables. All data analyses of the process evaluation will be descriptive and explorative.

Ethics and dissemination: Data collection, storage and evaluation meet all applicable data protection regulations. The trial has been approved by the Ethics Committees of the University of Wuppertal and the Medical Association of Saarland, Germany. Results will be disseminated through workshops, peer-reviewed publications, and local and international conferences.

Registration: DRKS00025485

Keywords

Patient safety, Medication Therapy Management, hospitals, clinical decision support systems, polypharmacy, evaluation/outcome and process assessment, stepped-wedge design, randomised controlled trial

ARTICLE SUMMARY

Strengths and limitations of this study:

- The TOP study is a randomised controlled trial in a stepped-wedge design that will provide evidence on the effects of a clinical decision support system (CDSS)-based intervention for medication management in inpatient care on patient-relevant outcomes.
- We hope to gain extensive insights into the effects by using different linked data sources; in particular, claims data from two statutory health insurance providers (SHIPs), self-reported patient data, and CDSS software data.
- In addition, the study will conduct a comprehensive process evaluation to provide insights into the implementation process, barriers to and factors facilitating implementation, and embedding activities in routine care.
- Due to convenience sampling at hospital level, it may be that the hospitals participating in the study are already more receptive to medication therapy management (MTM) and aware of the technical possibilities for its realisation compared to other hospitals in Germany.
- Since some hospitals have already established programmes for MTM, they start with better preconditions than others, potentially influencing various study endpoints; the comparability of study groups will be addressed by (1) collecting data on the primary endpoint from a pre-observational period and (2) collecting information on established measures in the hospital, allowing for the development and utilisation of appropriate control variables in the analysis.

INTRODUCTION

Polypharmacy, mostly defined as the concurrent use of at least five medications daily [1], is associated with an increased risk of adverse outcomes, including mortality, hospitalisation, adverse drug reactions, drug-drug interactions, medication non-adherence, and high health care costs [1-6].

The overall prevalence of polypharmacy is estimated at 37% [3], with a slightly lower estimate of 30% reported for Germany [4]. This prevalence varies not only between countries but also between different health-care settings and population age groups. Polypharmacy becomes more common with advancing age and the presence of multimorbidity. In the hospital setting, the prevalence of polypharmacy is noticeably higher, at 52%, compared to the community (20%) and outpatient settings (37%) [3, 4].

During transition from outpatient to inpatient care, there often are information gaps, potentially leading to avoidable harm. Adequate and safe decisions on diagnostics and therapy in hospital require full knowledge of a patient`s medical history and the outpatient treatment received [7-9]. In addition, prescription errors are often not recognised on admission to hospital, and medication errors in hospitals occur frequently [10-14]. Besides these, an inadequate transfer of information or inadequate coordination between different care providers after discharge from hospital can also lead to complications [8, 15]. Overall, hospitalisation is associated with an increased risk for patients' medication therapy [7, 8, 16].

To enhance the appropriateness of medication therapy management (MTM) during hospital stays, computerised interventions have shown promise with regard to patient safety. Clinical decision support systems (CDSS), as one of the IT-based interventions, are recognised as a promising approach to improve process-related outcomes such as, e.g. prescription, drug-drug interaction. However, there is limited evidence of the effects on patient-level outcomes such as readmission and mortality [17-23].

The TOP study ("*Transsektorale Optimierung der Patientensicherheit*" or "trans-sectoral optimisation of patient safety") will implement a complex CDSS-based intervention to optimise the process of inpatient medication therapy at admission, during the patients' stay in hospital, and at discharge, to prevent inappropriate medication use and thus promote patient safety.

AIMS

The primary objective of TOP is to optimise the process of medication therapy for inpatients at admission, during the patients' stay in hospital, and at discharge, in order to improve MTM and to achieve related outcomes such as a cross-sectoral improvement in quality, safety, cost-effectiveness and coordination of medication therapy, as well as increasing patient autonomy and self-management skills for inpatients with polypharmacy. We will demonstrate whether this complex intervention can contribute to an improvement of care using the example of the statutory health insurance system in Germany.

Therefore, the TOP trial aims to:

1. Evaluate the effectiveness of the complex intervention: we will examine whether the intervention reduces mortality and readmissions in polypharmacy patients treated in hospital. Furthermore, we intend to assess the impact of the intervention on inappropriate prescriptions, and severe and avoidable adverse drug events, as well as the utilisation of outpatient emergency care.

2. Evaluate the cost-effectiveness of the intervention: we will determine incremental cost effectiveness ratios (ICER); in particular, the cost per avoided hospitalisation and/or death and the cost per quality-adjusted life year from a payer's perspective.
3. Evaluate patient-reported outcome measures (PROs) such as health-related quality of life, and patient-reported experience measures (PREMs) such as experienced continuity of (pharmaceutical) care and patient satisfaction with information about medication. These measures will be collected to complement the claims data-based assessment of effectiveness from the patient's perspective.
4. Conduct a socio-economic impact assessment to support sustainability planning for spreading and scaling up the TOP intervention.
5. Evaluate the implementation process and its outcomes in participating hospitals and assess factors hindering and facilitating the implementation of digital interventions.

METHODS/DESIGN

This study protocol was written in accordance with the SPIRIT reporting checklist [24] (online supplementary material, file 1).

Study design

The intervention will be evaluated in a prospective, cluster-randomised controlled trial (C-RCT) using a stepped-wedge design (SWD) with an observation period of 33 months (30 months for recruiting + 3 months` follow-up of the last patient to be included) running from August 2021 to April 2024. The trial is designed as a hybrid type-1 effectiveness-implementation study addressing, besides effectiveness as the primary focus, the implementation of the TOP intervention as well [25]. A total of 12 hospitals will be randomly assigned to three clusters. Each cluster starts in a control phase. The intervention will then be introduced to each cluster with a time delay (i.e. in steps), similar to a unidirectional cross-over design (see Figure 1). The patients will be treated according to the group status of the hospital and, depending on that group status, receive either standard care (control phase) or the TOP intervention (transition and intervention phase). The study design allows the recording and comparison of temporal effects as well as an intensive process evaluation.

The intervention represents a novel process currently undergoing untested implementation within the hospital setting. Therefore, two hospitals accompanying the study are responsible for testing and optimising the acceptability, appropriateness and feasibility of the intervention and its implementation. In addition, these test hospitals play a crucial support role for the hospitals involved in the C-RCT, helping them to successfully implement and embed the TOP intervention.

	C-RCT (33 months)					
	month 1-6	month 7-12	month 13-18	month 19-24	month 25-30	month 31-33
	tests at two accompanying hospitals					
cluster 1	control phase	transition phase	intervention phase			follow-up
cluster 2	control phase		transition phase	intervention phase		follow-up
cluster 3	control phase			transition phase	intervention phase	follow-up

Figure 1 Roll-out including follow-up of the C-RCT in a stepped-wedge design

Setting, participants and recruitment

Study setting

The study will be carried out in 12 hospitals across Germany. These will include hospitals in different states, of different sizes, with different ownership structures, and with departments relevant to the study (see Inclusion criteria). Each participating institution must give its consent by signing a cooperation agreement.

Inclusion and exclusion criteria

Hospital level

Hospitals can participate in the study if they are willing to hire a pharmacist for the duration of the study or to assign the study tasks to a suitably qualified member of staff. Furthermore, the hospital should be willing to assign staff to study-related tasks, such as informing and enrolling patients willing to participate, for the duration of the C-RCT. Hospitals that are already participating in a similar project will be excluded.

Staff level

Healthcare professionals (HCPs): The HCPs in the study will be pharmacists (ward or hospital pharmacists, depending on the existing structure of the hospital) and physicians from the participating departments who are directly or indirectly involved in the TOP intervention. Additionally, each participating hospital provides key persons (e.g. project manager at the hospital, head of pharmacy and of the specialised department) as a responsible key informant on the implementation process.

Patient level

Included in the trial will be all patients aged 18 years and over and insured with participating health insurance providers (BARMER and AOK Nordost) who take at least five prescribed drugs and were initially hospitalised in a participating hospital's department of internal medicine, geriatrics, visceral surgery, vascular surgery, cardiac and thoracic surgery, orthopaedics and trauma surgery, neurology, or urology during the study period. Inclusion in the study will be consecutive. Patients undergoing oncological treatment will be excluded due to regular hospitalisation based on treatment cycles.

Recruitment of hospitals and study participants

Hospital level

Hospitals are recruited nationwide, the aim being to recruit hospitals from several states, of varying size and, if possible, having the departments relevant to the study. The hospitals participating in the trial are based on a convenience sample.

Staff level

At the beginning of the trial, hospitals will designate key informants, who will be invited to participate in the data collection of key persons. In order to survey all HCPs (complete enumeration), medical and pharmaceutical staff will be recruited via key persons in the organisation concerned. They will also hand out the survey documents. Before taking part in data collection, all persons will receive written information about the surveys.

Patient level

Patients will be recruited at participating hospitals and will be assigned to the control, transition or intervention phase, depending on the hospital's study phase. All patients who meet the inclusion criteria will be invited to participate in the TOP study by pharmacists during their admission as an inpatient. Patients will be provided with written information and must give their consent in order to participate in the study. Although patient recruitment in the hospitals started in August 2021 (month 1), participant enrolment did not start until November 2021. The start was delayed (compared to the start of the C-RCT) because the recruitment process and the transfer of patient information to the SHIPs had to be introduced and established in the study hospitals, and the processes for checking patients' inclusion criteria and sending study documents to patients by the SHIPs had to be adapted. This had to be based on the existing structures and processes of healthcare practice and could therefore only be tested and adapted after the start of the C-RCT. The recruitment period ends on the last day of the intervention phase for all hospitals (month 30).

Randomisation

Randomisation takes place at the hospital level, i.e. at the start of the project, all participating hospitals are randomly assigned to a cluster. Randomisation will be stratified based on the hospitals' size (determined by number of beds and cases) to ensure that the numbers of control and intervention patients are balanced. There will be no randomisation at patient level, as it is assumed that the service providers in the hospitals will experience learning effects, which would then influence the treatment of patients from the control group.

Intervention

Description of the intervention

The TOP intervention is a complex intervention that focuses on intensified pharmaceutical care for patients on admission to hospital, during their inpatient stay, and on discharge. MTM is a key component of the intervention and will be carried out electronically using CDSS-based software. A detailed description of the several interdependent components of the intervention based on the TIDieR Checklist [26] is given in Table 1, Components of TOP intervention (online supplementary material, file 2).

Implementation of the intervention

The intervention will be implemented in a time-lagged design in participating hospitals. Over the course of the study, each hospital will pass through the control period, the transition period, and the intervention period. For validating effectiveness, it is crucial that certain actions of implementation are realised in the appropriate period and completed before transitioning into the next period. Preparatory actions at the hospital, such as finalising the technical connection or hiring/internally assigning a pharmacist, will take place before or during the control period. Here, only actions that do not influence the care process may be carried out. During the transition period, the intervention will be introduced and "rehearsed" in the facility concerned for the first time. This period constitutes a testing phase during which, for example, it is still possible to make procedural adjustments. This transition period is followed by the intervention period, in which the intervention will be fully realised under everyday conditions.

Multicomponent implementation strategies will be carried out to enhance the implementation process and the outcomes (e.g. fidelity) of the TOP intervention in routine care. The initial implementation strategies in TOP cover the elements of providing interactive assistance, developing stakeholder interrelationships, training and educating stakeholders, engaging consumers, utilising financial strategies, adapting and tailoring the TOP intervention to the context, and using evaluative and iterative strategies based on the Pragmatic Implementation Strategy Reporting Tool [27]. For details of the implementation strategies, see Table 2 Implementation strategies of TOP (online supplementary material, file 3).

Outcome assessment

Primary outcome

The primary outcome, based on health insurance claims data is the combined endpoint of all-cause mortality and all-cause hospitalisation in polypharmacy patients three months after discharge.

Secondary outcomes

The primary endpoint is followed by several secondary endpoints regarded as significant for the overall success of the intervention. In detail, these include the effectiveness and cost-effectiveness of the intervention regarding the following aspects:

1. Percentage/proportion of patients who receive inappropriate prescriptions and percentage/proportion of patients who suffer from severe and avoidable adverse drug events at the hospital or within three months post-discharge (based on claims data).
2. Utilisation of different health services such as emergency care (based on claims data).
3. Cost-effectiveness and cost-utility of the intervention compared to standard care (based on claims data and survey data).
4. Patient-reported outcome and experience measures (PROMs and PREMs) will be collected by questionnaire at two measurement points: shortly after discharge from hospital (t0) and approximately 90 days after discharge (t1). PROMs and PREMs will include adverse drug events [28] (t0 & t1), experienced continuity of (pharmaceutical) care [29] (t0 & t1), satisfaction with information about medicines [30] (t0 & t1), adherence [31] (t0 & t1), patient enablement/empowerment [32] (t0 & t1), patient safety [33] (t0) and health-related quality of life [34, 35] (t0 & t1).
5. Costs and benefits (financial, resources/time, intangible) of the intervention at the level of stakeholders and the service overall (based on claims data, software routine data, survey data).

Process evaluation

A process evaluation will be conducted to understand the intervention effects of complex interventions such as TOP and to identify their potential for generalisability and possible improvement [36]. The process evaluation will therefore involve the scientific monitoring of the intervention throughout the duration of the planned C-RCT and address questions of a process-descriptive or organisational-change nature. The evaluation will follow the Medical Research Council's recommendations for process evaluations of complex interventions [37], be guided by the framework established by Grant et al. [38] for monitoring cluster-randomised controlled trials, identify effect-modifying factors, and focus on exploring mechanisms of impact. The process evaluation of TOP will include different data collection methods (written questionnaires, interviews, document analysis of field notes and software data) from different target groups (pharmacists, physicians, patients). Data will be collected on context, recruitment, implementation, mechanism of impact, and effectiveness throughout the duration of the C-RCT. The data collection time points at the organisational level will be determined by the hospital's affiliation with one of the three switching cohorts. More detailed information on the data collection of process evaluation is given in Table 3, Data collection of process evaluation (online supplementary material, file 4).

DATA COLLECTION AND MANAGEMENT

Data collection

Secondary data/claims data from participating health insurance providers

Claims/routine data from August 2021 to April 2024 will be used in the analysis. Data collection is therefore longitudinal and data will be available for the duration of the C-RCT, as well as the pre-observation period so as to establish a baseline for the primary endpoint.

The required claims data from participating health insurance providers are specified in a coordinated minimal data set. Variables included in the dataset are sociodemographic patient data (sex, age, insurance status, reason insurance coverage ended), outpatient diagnoses and outpatient services (ICD-10 diagnoses, services according to the physician's fee scale), medication (pharmaceutical registration number, ATC code, duration of the therapy (DDD), costs), inpatient data (start and end date of each hospitalisation, admission and discharge diagnoses, secondary diagnoses, operation and treatment procedures, costs), long-term nursing care (start and end date, level and place of care, costs and type of service), incapacitation for work (ICD-10, start and end, costs), ambulance services (start and end).

Primary data

Primary data will be collected from patients treated with the intervention (transition and intervention phase) as well as those who have confirmed their willingness to participate in the data collection (control phase) and are able to consent. Data will be collected through a questionnaire sent by post. All survey participants who have agreed to be contacted by the health insurers after hospitalisation and who meet the inclusion criteria of the survey will be contacted. This procedure was chosen to ultimately achieve a response rate of at least 25% of all study patients. The questionnaires will be delivered by the health insurance providers and will be returned to the University of Wuppertal. Once the pseudonymised questionnaires arrive at the University of Wuppertal, they will be scanned in.

To monitor implementation status and possible obstacles to the implementation of the intervention, the hospitals will be asked to report any unexpected events every 3 months. These are events at the individual level (e.g. illness of the staff responsible), ward level (e.g. staff shortages) and hospital level (e.g. strike). The survey will be sent to the contact persons in the hospitals via e-mail.

Data from the software solution

For the data from the software solution for evaluating the secondary endpoints (medication plans) and user behaviour (process evaluation), an MDS is coordinated with the operator of the software, enabling the corresponding evaluations. Data from the software solution include e.g. information about boxes clicked within the software by the pharmacists, such as "Medication therapy

recommendation set", "Pharmaceutical discharge interview done", "Printed handout on medication therapy given to patient", the medication the patients take, interactions, and alerts.

Data from process evaluation

The collection process for the data from process evaluation will depend on the type of data collection. Qualitative data will be collected through face-to-face or telephone interviews from a subsample. A structured guide will be used during the interviews. All interviews will be recorded and subsequently transcribed according to appropriate guidelines [39]. In the case of written surveys of staff (medical, pharmaceutical), the aim is to conduct a full survey. The questionnaires will be created using Teleform® and sent to the healthcare professionals by the responsible evaluation partner (BUW). Delivery of questionnaires to patients (T0 and T1) for collecting data for the process evaluation is identical to the data collection process for primary data. All completed questionnaires will be sent back to the responsible evaluation partner (BUW). Once received, the pseudonymised questionnaires will be scanned and digitised.

For the document analysis, field notes used during the introduction and implementation of the intervention or created during the evaluation will be collected. They may include e.g. training protocols and hospital implementation guides. Hospitals will provide copies of documents to the responsible evaluation partner (BUW) for analysis or grant access for data extraction. The method of document analysis will help identify e.g. factors supporting or hindering the implementation process.

The data collected, including interview transcripts, questionnaire responses, and documents will be processed using established software tools commonly used in the social sciences. These tools include SPSS, R, and MAXQDA, which allow for a thorough analysis and interpretation of the data.

Data management

The evaluation consists of two study sections, with study section 1 using only claims data at the population level, and study section 2 using claims data from participating SHIPs, primary data, and medication plan data from the software used, all at the study participant level (see Figure 2).

The primary endpoint will be evaluated using claims data from the participating SHIPs at the population level (all potential patients in the hospital, intention-to-treat, study section 1). Both SHIPs will select records for the relevant observation periods in participating wards of participating hospitals, based on the inclusion criteria of a minimum age of 18 and being prescribed three or more drugs. To estimate a baseline of MTM measures, characteristics of the primary endpoint in participating hospitals will be calculated from a pre-observation period using this dataset.

The secondary endpoint is based on multiple endpoints with a linkage of primary and secondary data (individual study participant level, per-protocol, study section 2). The secondary endpoint will be

divided into the analysis of patients enrolled and treated, and patients enrolled in the control phase and receiving standard care. For patients in the control phase, claims data, primary data at the individual level (patients) and primary data at the organisational level (hospital) will be linked. The linkage of the primary data at the individual level, the software data and the claims data will be done using a pseudonym for each patient. An institutional pseudonym will be assigned to the primary data at the organisational level, collected for the formative evaluation/process evaluation for matching with the hospital concerned.

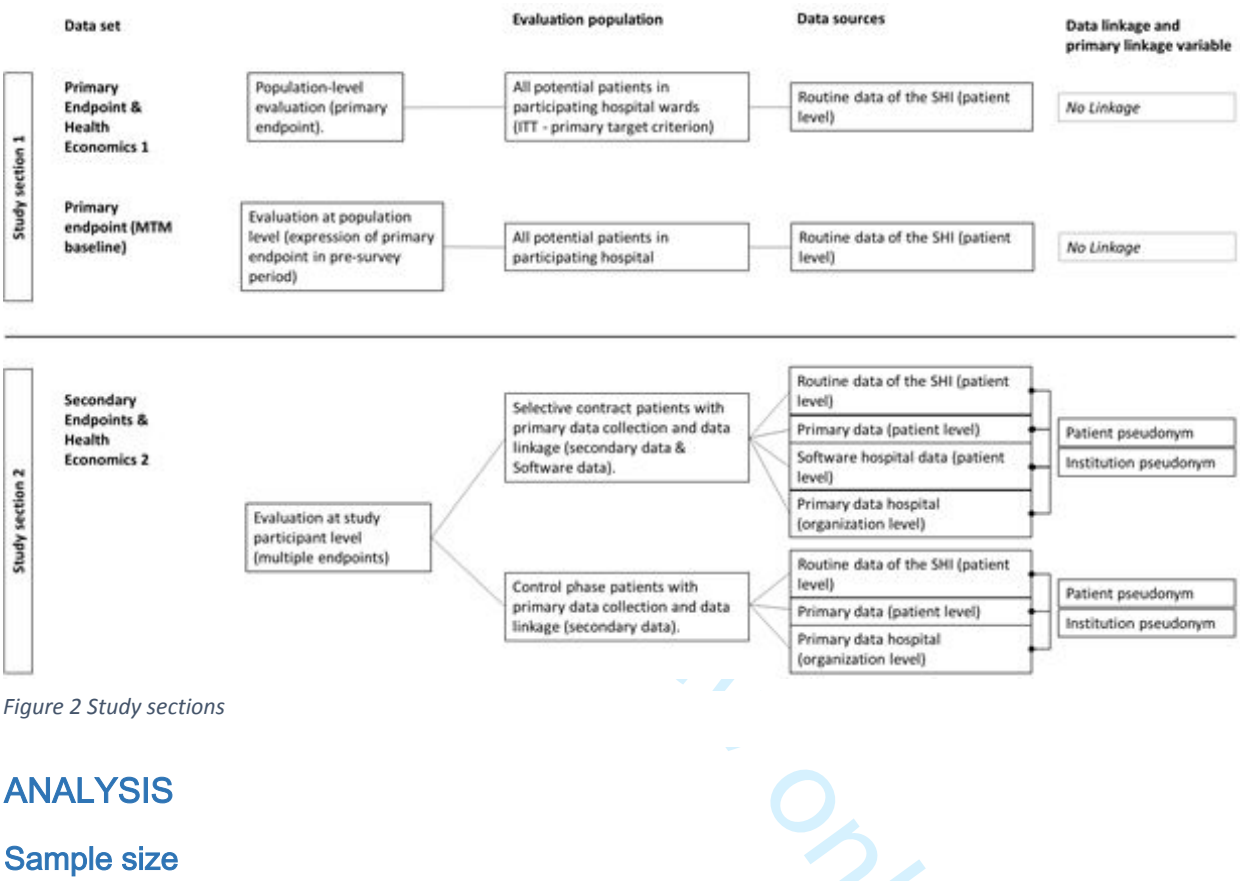

Figure 2 Study sections

ANALYSIS

Sample size

According to a preliminary analysis based on BARMER routine data, the incidence of readmission or death within 90 days from initial hospitalisation is 32.9% (24.81% readmission <90d; mortality 2.66% in hospital, 5.43% <90d after discharge). Assuming a 15% reduction of the primary combined endpoint to 27.97%, an α-error of 0.05, and a power of 1-β=0.80, the underlying regression model yields a sample size of 146 treated patients, or cases per hospital per time interval (quarterly period). With 12 hospitals participating over 8 quarters (30 months excluding the transition phase), the total number of patients treated is aimed to be 14,016 (7,300 for the control phase and 6,716 for the intervention phase). An expected dropout rate of 40% increases the sample size to 23,328, with 243 patients to be recruited per hospital per quarter. To evaluate the implementation appropriately in the process evaluation, an additional 5,832 patients should be recruited for the transition phase in the 12 hospitals.

This sample size was calculated using an intra-class correlation coefficient (ICC) of 0.05, which had been determined in the preliminary analysis of the BARMER data.

Analysis of primary and secondary outcome parameters

The primary objective of this study is to determine whether this complex intervention reduces the combined endpoint of all-cause mortality and all-cause hospitalisation in adult patients with polypharmacy 90 days post-discharge.

The evaluation strategy for the primary endpoint is based on study section 1, including all patients insured with participating health insurance providers who were hospitalised in a participating hospital during the study period and fulfil the inclusion criteria. In this way, not only the effects of the intervention on patients treated with this new form of care are taken into account, but also access to the intervention and spill-over effects regarding the treatment of non-participating patients. In subordinate analysis, group comparisons will be made, in which selective contract participants are to be compared with control group patients as a subgroup.

Statistical analysis will be conducted for primary and secondary endpoints (study section 1 and study section 2) at cluster level, in the form of within-cluster and between-cluster analyses. First, the primary and secondary endpoints will be analysed descriptively. The statistical analysis will use (generalised) linear mixed models ((G)LMM) [40] or generalised estimating equations (GEE) [41, 42], taking account of independent covariables (e.g. age, gender, hospital). The results of the survey of unexpected events will be included in the analysis as confounders to control for possible effects of these events. For the analysis of study section 2, medication plan data from the software will be included in addition to the confounders available in the claims data.

Primary patient level data analysis will be descriptive and exploratory. The statistical analysis will follow the procedures used for the routine data.

Cost-effectiveness analysis

The health economic analysis will be conducted from a third-party payer perspective, which is the perspective of the SHIPs in Germany. The incremental cost-effectiveness ratio (ICER) will be calculated by dividing the difference in costs by the difference in health benefit of the intervention compared to standard care. The analysis of all reimbursed direct health care costs will be based on health insurance claims data comprising healthcare resource utilisation regarding inpatient care, outpatient care, rehabilitative care, pharmaceuticals, therapeutic devices, non-physician specialist services, nursing (home) care, and patient transport services, and sick pay. Intervention-related costs will also be included. Benefits of the intervention will be measured by the primary outcome (hospitalisation and/or death) and the secondary outcome of health-related quality of life. Hence, the cost per avoided

hospitalisation and/or death (CEA, cost-effectiveness analysis) and the cost per QALY (quality adjusted life year) (CUA, cost-utility-analysis) will be analysed.

The CEA will be based on the population level (see section data collection). However, for the CUA, data obtained by the EQ-5D-5L [35] collected in the C-RCT will be used to calculate QALYs by using the German value set [43] . Thus, the CUA will be based on a reduced sample.

Socio-economic impact assessment

In order to support sustainability planning of the intervention for transfer into regular care, a socio-economic impact assessment (SEIA) will be conducted. It is a formative evaluation that aims to answer questions on three levels (see Figure 3):

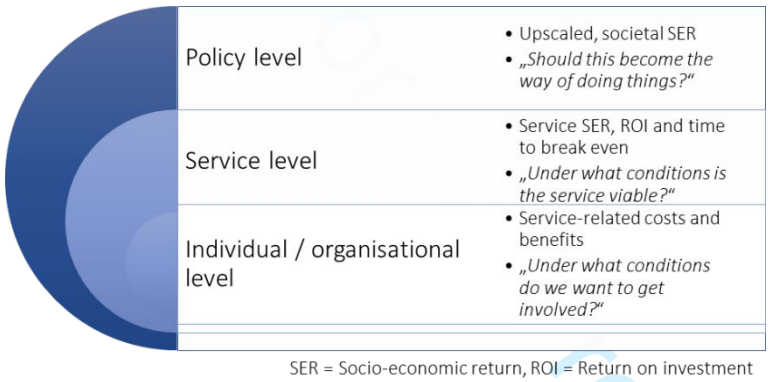

Figure 3 Socio-economic Impact Assessment (SEIA) - addressed levels

Methodologically, SEIA is based on cost-benefit analysis as defined by Drummond [44] and the recommendations of UK HM Treasury [45], the Federal Government Commissioner for Information Technology [46] and the White House Office for Management and Budget [47]. An already established framework and associated evaluation software developed for business model development for IT-based utility services will be used [48].

Process evaluation

All data analyses of the process evaluation will be descriptive and explorative. The analysis of qualitative data material will be either content analysis or a qualitative-descriptive analysis. In analysing the interviews, a deductive procedure will be followed initially, in which paraphrases from the interviews are assigned to themes and sub-themes of the underlying frameworks or theories of the respective data collection (e.g. CFIR, normalisation process theory). Within the themes and sub-themes, the content will be processed inductively. The analysis of the questionnaire and software data will be descriptive and exploratory.

PATIENT AND PUBLIC INVOLVEMENT

This protocol was developed without patient or public involvement.

ETHICS AND DISSEMINATION

The TOP study was approved by the Ethics Committees of the University of Wuppertal (no. MS/AH 201028) and the Medical Association of Saarland, Germany (no. Ha 37/21). In case of important modifications of the protocol, the afore-mentioned Ethics Committees and the funding institution will be informed immediately.

Written informed consent will be obtained from the managers of each participating hospital through their signing a supply contract. Healthcare professionals will receive comprehensive information on the study before getting involved in data collection. The staff can stop data collection at any time if they wish.

Written informed consent will be obtained from all participating patients if they decide to get involved in the study during their hospital stay (individual study participant level, study section 2). A two-stage process has been developed for consent to participate in the study. Consent to participate in the study is only valid after the participant has read the information, had the possibility to ask questions and signed the informed consent for participation in the study (during the hospital stay) and the informed consent for the scientific monitoring and evaluation of the study (after the hospital stay). For model consent forms, see the online supplementary material, file 5. Any participant may withdraw their consent at any time. The data of study section 1 (claims data at the population level) are provided on the grounds that it would be unreasonable to obtain the consent of all patients insured with the participating SHIPs. These grounds include, among other things, the relevance of the study to the general population and the risk of bias due to selection effects when consent is obtained.

A declaration of consent permitting data access is a prerequisite for retrieving patient-related information from the health insurance providers. The software documents which registered user of the hospital information system has retrieved or processed information, and on which patient and at what time.

When the software is installed, a key encrypted by a fixed code and managed in the software is generated, i.e. only the software knows the patient-related data. Only authorised hospital staff can access the data stored. Neither the health insurance nor the software provider can view the treatment data.

BARMER and the hospitals accompanying the study will be responsible for monitoring the trial, and in particular for recruiting hospitals and supporting patient recruitment and the implementation of the intervention by the study hospitals. The monitoring of BARMER includes e.g. to perform random checks of whether a valid declaration of consent exists for insured patients whose health insurance data have been retrieved for treatment support. The steering committee, consisting of members of the TOP

study group, will meet via telephone conferences twice a month to review the progress of the study and to make decisions within the framework of the study if necessary. The participating SHIPs, the study hospitals and the software provider will be responsible for providing data to the evaluation team. A designated advisory board will provide advice on the design, conduct and analysis of the trial. The data monitoring committee, consisting of members of the SHIPs, the hospitals accompanying the study, the software provider and the evaluation team, will be independent of the institution funding the study and of competing interests.

Results of the study will be disseminated through publications in international, peer-reviewed journals and conference contributions. The reporting of the results will adhere to the CONSORT Statement extension for cluster-randomised trials [49].

Trial status and registration information

Hospital recruitment began with the project's start in October 2020. Start of the C-RCT was August 2021, while the first participant enrolment was planned for 15/09/2021 and has started in November 2021. The last patient in will be at the end of January 2024 and the 3-month follow-up will be accordingly completed at the end of April 2024. Data collection will be completed by the end of August 2024. Analyses will be completed in September 2024.

Registration of the trial was initiated before the start of the C-RCT (August 2021), displayed on the public website after the start of the C-RCT (09/09/2021) but before the date of the first enrolment of participant (planned for 15/09/2021, with the first valid enrolment in November 2021).

ABBREVIATIONS

ATC code	Anatomical Therapeutic Chemical code
BUW	Bergische Universität Wuppertal
CDSS	Clinical decision support system
CEA	Cost-effectiveness analysis
CFIR	Consolidated Framework for Implementation Research
CONSORT	Consolidated Standards of Reporting Trials
C-RCT	Cluster-randomised controlled trial
CUA	Cost-utility-analysis
DDD	Defined daily dose
GEE	Generalised estimating equations

(G)LMM	(Generalised) linear mixed models
HCP	Healthcare professionals
ICC	Intra-class correlation coefficient
ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental cost-effectiveness ratio
IT	Information technology
MTM	Medication therapy management
PREMs	Patient-reported experience measures
PROMs	Patient-reported outcome measures
SEIA	Socio-economic impact assessment
SHIPs	Statutory health insurance providers
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SWD	Stepped-wedge design
TIDieR	Template for intervention description and replication
TOP	Transsektorale Optimierung der Patientensicherheit

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DISCLAIMER

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

AVAILABILITY OF DATA AND MATERIALS

Data collection forms and datasets generated and analysed during the current study are not publicly available, as participant consent and German regulatory instances restrict data use to the research team but they are available from the corresponding author on reasonable request and with permission of all involved institutions.

AUTHOR CONTRIBUTIONS

RB drafted the first version of the manuscript with input from JK-N and SM. Critical revision of manuscript for important intellectual content: SS, DL, AP, IM and JK-N. SM, DL, AP, DG, CK, IM, WG, JK-N, are responsible for study concept and design. AD is the study director. Acquisition of data: SM, SS,

DL, AP, PI, IM, WG, JK-N and TOP study group. Analysis and interpretation of data will be performed by SM, SS, DL, AP, IM, WG, JK-N. PI is responsible for data management and the trust centre. JK-N is the chief investigator of the study. All authors reviewed the paper and read and approved the final manuscript.

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COMPETING INTERESTS

SM, DL, PI, SS, CK, AD, KCR, IM, WG, JK-N 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 a family member of DG 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.

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	C-RCT (33 months)					
	month 1-6	**month 7-12**	**month 13-18**	**month 19-24**	**month 25-30**	**month 31-33**
	tests at two accompanying hospitals					
cluster 1	*control phase*	*transition phase*	*intervention phase*			follow-up
cluster 2	*control phase*		*transition phase*	*intervention phase*		follow-up
cluster 3	*control phase*			*transition phase*	*intervention phase*	follow-up

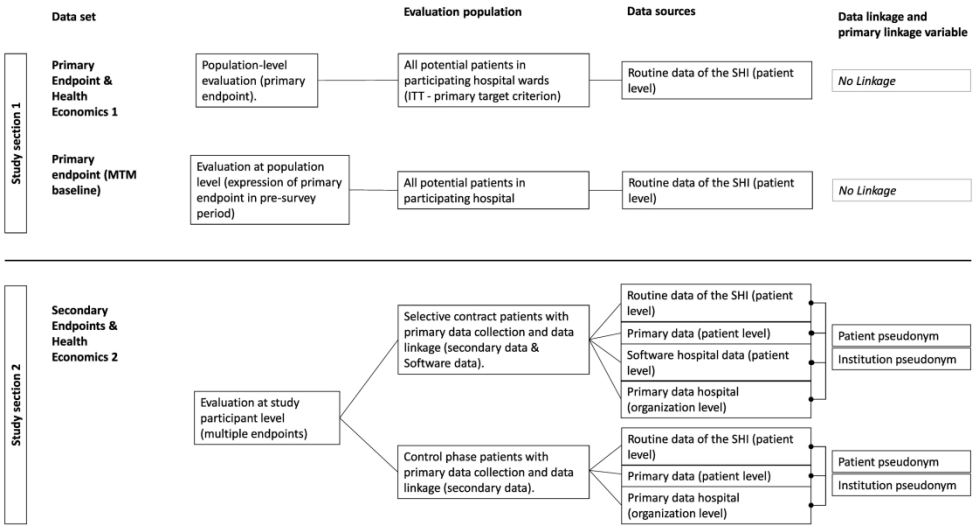
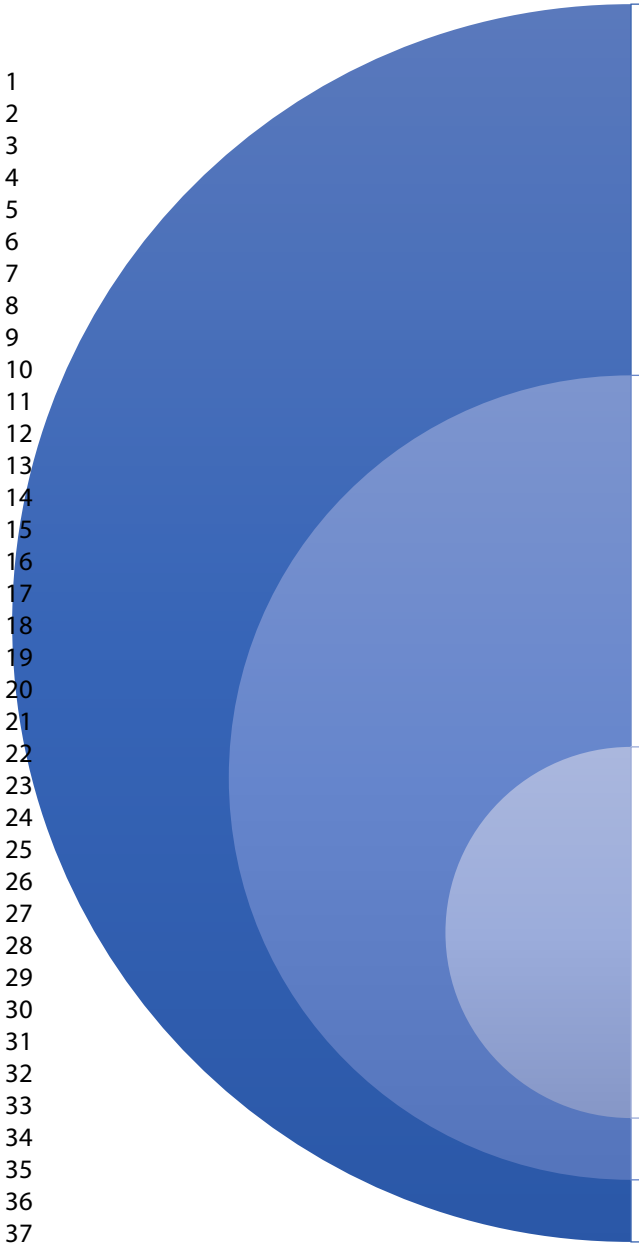


Figure 2 Study sections

297x164mm (300 x 300 DPI)



Policy level	• Upscaled, societal SER • *„Should this become the way of doing things?“*
Service level	• Service SER, ROI and time to break even • *„Under what conditions is the service viable?“*
Individual / organisational level	• Service-related costs and benefits • *„Under what conditions do we want to get involved?“*

SER = Socio-economic return, ROI = Return on investment

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Check
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	✓ *(p.1)*
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	✓ *(p.3)*
	2b	All items from the World Health Organization Trial Registration Data Set	✓
Protocol version	3	Date and version identifier	✓ *(p.19)*
Funding	4	Sources and types of financial, material, and other support	✓ *(p.18)*
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	✓ *(p.18)*
	5b	Name and contact information for the trial sponsor	✓ *(p.18)*
	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	n.a.
	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)	✓ *(p.16)*
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	✓ *(p.4-5)*
	6b	Explanation for choice of comparators	✓ *(p.4-5)*
Objectives	7	Specific objectives or hypotheses	✓ *(p.5-6)*
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)	✓ *(p.6-7)*
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	✓ *(p.7)*

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)	✓ *(p.7-8)*
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	✓ *(p.8-9 & online supplemental 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)	n.a.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n.a.
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n.a.
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	✓ *(p.9-10)*
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)	✓ *(p.7,9-10 & online supplemental file 2 & 4)*
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	✓ *(p.13)*
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	✓ *(p.7-8)*
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	✓ *(p.8)*
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	n.a.
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	✓ *(p.8)*
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n.a.
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n.a.
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	✓ *(p.10-12)*
	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	n.a.
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	✓ *(p.12-13)*
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	✓ *(p.13-14)*
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	✓ *(p.13-15)*
	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)	n.a.
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	✓ *(p.16)*
	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	n.a.
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	✓ *(p.11)*
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n.a.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	✓ *(p.15-16)*
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)	✓ *(p.15)*
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	✓ *(p.16)*
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
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	✓ *(p.12)*

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	✓ *(p.18-19)*
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	✓ *(p.18)*
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	n.a.
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	✓ *(p.16)*
	31b	Authorship eligibility guidelines and any intended use of professional writers	✓ *(p.18)*
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n.a.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	✓ *(online supplemental 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	n.a.

*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.

Table 1 Components of TOP intervention

Brief name	What?	Why?	How?	Who?	Where?	When and how much?
Electronically available treatment-relevant information at hospital admission	Anamnesis support on admission	Recognising inadequate outpatient pretherapy, avoiding errors in anamnesis	Making treatment-relevant information electronically available from health insurance data	Pharmacist (ward pharmacist or hospital pharmacist)	Access by computer using the TOP software in all parts of the participating hospital admitting patients (accident & emergency services, wards, pharmacy)	Once, when patient is admitted to hospital
MTM at hospital admission	Structured medication review on admission	Recognising prescription errors, correctly interpreting adverse drug reactions, reduction of prescription cascades, avoidance of treatment errors due to missing information	Electronically supported MTM review with subsequent recommendation for correcting inadequate medication therapy, medication reconciliation (between patient self-reports and health insurance data), documentation and communication of possible or necessary adjustments of medication	Pharmacist (ward pharmacist or hospital pharmacist), physician in patient`s department	Access by computer using the TOP software in all parts of the participating hospital admitting patients (accident & emergency services, wards, pharmacy) Communication of adjustments to medication therapy through hospital information systems, by email or phone	Once, when patient is admitted to hospital

MTM during hospital stay	Co-care of high-risk patients during their hospital stay	Improving MTM in the hospital, reducing mortality and complications in the hospital, avoidance of treatment errors	Electronically supported MTM review for inpatient medication therapy of high-risk patients	Pharmacist (ward pharmacist or hospital pharmacist)	By computer using the TCP software	Daily during patient`s hospital stay
MTM at discharge from hospital	Medication checking and recommen-dation of medication therapy at discharge	Reducing medication errors	Electronically supported MTM review with subsequent recommendation for correcting inadequate medication therapy, documentation and communication of possible or necessary adjustments to medication, comparison of the final therapy recommendation to previous medication	Pharmacist (ward pharmacist or hospital pharmacist), physician in patient`s department	By computer using the TCP software Communication of adjustments to medication therapy through hospital information systems, by email or phone	Once before patient is discharged

Medication information of patients at discharge from hospital	Patient empowerment at discharge	Informing the patient about medication after discharge to improve health literacy, autonomy and adherence, reducing application errors	Pharmaceutical discharge interview (face-to-face) including information about BMP (printed handout of medication therapy), information regarding supplemental self-medication, therapy supporting notes via app	Pharmacist (ward pharmacist or hospital pharmacist)	The interview takes place in the patient`s room or in a room of the department or pharmacy	Once before patient is discharged
MTM-coordination at discharge from hospital	Cross-sectoral coordination at discharge	Reducing medication errors and avoiding information breaches between sectors, avoidance of treatment errors due to insufficient cross-sectoral coordination	Coordination of changes to therapy with the general practitioner who continues treatment	Pharmacist (ward pharmacist or hospital pharmacist), general practitioner	Communication of adjustments to medication therapy through information systems, by email or phone	If necessary, once before patient is discharged

MTM: medication therapy management

Table 2 Implementation strategies of TOP

Name it: ERIC Implementation strategy	Operationalise it								
	Action	Actor	Context	Dose	Action Target		Temporality	Implementation Outcome	Justification
					Conceptual	Unit of Analysis			
Use evaluative and iterative strategies									
Assess for readiness and identify barriers and facilitators	Assessing facilitators for and barriers to implementing the TOP intervention through collected field notes and assessment of determinants of implementation (e.g. resources and attitudes of healthcare professionals - HCPs) through written questionnaires	HCPs (physicians and pharmacists) in the hospitals for data collection through questionnaires, TOP study team for collecting field notes and analysis of the data collected	Assessment and analysis electronically, written questionnaire is sent to the HCP to fill in during the hospital shift	Field notes are collected continuously, data collection with HCP through written questionnaire twice during the study	Context	Hospital-based	Field notes: transition and intervention phases; written questionnaire: control and intervention phases	Barrieres to and facilitators for implementing the TOP intervention	To analyse and control the organisation-related factors which may have an influence on the degree of TOP implementation and the outcomes measured in study setting.

Stage implementation scale-up	For implementing the TOP intervention, there are two hospitals accompanying the study, which will implement the intervention before the C-RCT starts.	Two hospitals accompanying the C-RCT	Pharmacists (and physicians) at the accompanying hospitals implement and test the TOP intervention in routine care	Implementation takes place once in each accompanying hospital	Assistance to implementation	Hospital-based	In the preparation phase of the study (10 months before C-RCT starts)	Barrieres to and facilitators for implementing the TOP intervention, necessary adaptations of TOP intervention and its implementation process	TOP is a complex intervention that is to be introduced into routine care for the first time in 12 hospitals. To optimse the implementation process and intervention itself before it is tested in the study.
Provide interactive assistance									
Centralise technical assistance	The two accompanying hospitals provide technical assistance on all issues of implementing the TOP intervention into routine care for hospitals included in the study if questions arise and support is needed.	Pharmacists at the accompanying hospitals in coorperation with the software developer/support team, pharmacists of study hospitals	Support is offered by phone, email and through online meetings	Support is offered as needed, online meetings once a week	Context, implementation and mechanism of impact	Hospital-based	Transition and intervention phase	Barriers and facilitators, adaptations, fidelity, feasibility, response	To support the study hospitals in the best possible implementation of the TOP intervention.

Adapt and tailor to context									
Promote adapta-bility	Tailoring the intervention to the given structures and processes of every study hospital (organisation-specific implementation-plans).	Pharmacists (and physicians) of the accompanying and study hospitals, TOP study team	Remotely by email, phone or in online meetings	Tailoring is offered as needed	Imple-menta-tion and effec-tiveness	Hospital -based	Transition and intervention phase	Adaptations to intervention, fidelity, acceptability	To implement the TOP intervention into routine care, it is necessary to observe and take into account the given stuctures and processes of every health facility because they may differ as a function of the size of the hospital, patients, processes etc..

Develop stakeholder interrelationships									
Organise clinician implementation team meetings	Build structures for an information exchange between the pharmacists (and physicians) at the study hospitals	Pharmacists (and physicians) and key persons at the accompanying and study hospitals, TOP study team	In online meetings, in person	Online meetings with pharmacists once a week, online meetings with study hospitals once a month, and if necessary, in-person meetings (once a year)	Implementation and mechanism of impact	Hospital-based	Transition and intervention phase	Acceptability, appropriateness, feasibility	Use of lessons learned can improve the implementation process and acceptability, appropriateness and feasibility of the intervention.
Train and educate stakeholders									
Conduct educational meetings	Educational meetings are held for key persons and HCPs on different topics (e.g. intervention details like process training, rules for reviewing indications for medication therapy, study details like evaluation of the TOP intervention)	TOP study team, key persons and HCPs at the two accompanying and study hospitals, software developer team	In online meetings, in person	Online meetings with pharmacists once a week, online meetings with study hospitals once a month and as necessary	Implementation	Hospital-based	Established early in the control phase of the C-RCT, maintained throughout the C-RCT	Fidelity, acceptability	Educational training is a necessary but insufficient strategy for behavioural change. Building knowledge is important for laying the foundation for the actual application of the intervention components.

Engage consumers									
Use mass media	Information on the TOP intervention is placed in newspapers, information materials (in print and online) by particpating statutory health insurance providers (SHIPs)	SHIPs, TOP study team	In print and online	Established early in preparation phase of the C-RCT, maintained over time	Recruit-ment and imple-menta-tion	Patient-based and hospital -based	Preparation and C-RCT phase	Recruitment and reach of intervention (patient-level)	Receiving information about the TOP intervention could improve patients` commitment to being involved in the study and thus improve the patient-related reach of the intervention.

Utilise financial strategies									
Use capitated payments	TOP intervention is part of a funded project of the G-BA, the hospitals receive financial support (e.g. amount per patient for an intervention delivered to the patient, hospitals receive funds for implementing the TOP software and hiring staff)	SHIPs, Funder: G-BA	Funds are transferred electroni-cally	Payments for financial support per patient are delivered depending on the number of patients recruited for the study, one-off payments for infrastructural support	Imple-menta-tion and mecha-nism of impact	Patient-based and hospital-based	Amount per patient: transition and intervention phase, infrastructural payment: transition phase	Reach of intervention (patient and hospital level), feasibility	Implemen-ting a new form of care is a highly complex process of change in the routine care of the hospitals, which are subject to financial pressure anyway. Financial support is necessary to optimise the implementa-tion and use of new interventions like TOP.

Table 3 Data collection of process evaluation

Focus	Assessment	Measurement point
Domain – Context: In which context and setting does the intervention take place? What are the determinants of implementation?		
Hospital level		
Hospital baseline data on organisational-structural conditions, e.g.: - Organisational structures and processes - Organisational culture - Organisational Readiness for Implementing Change	Written survey: key person at the hospital (e.g. management, project manager)	Control phase
Staff baseline data on organisational-personnel readiness, e.g.: - Professional background - Interprofessional collaboration - Organisational Readiness for Implementing Change - Acceptance and Use of Technology	Written survey: pharmaceutical and medical staff	Control phase
Patient level		
Patient baseline data, e.g.: - Socio-demographic data - Previous experience with MTM and components of the TOP intervention	Written survey: enrolled patients	Shortly after discharge from hospital (t0)
Domain – Context: What factors inhibit or promote implementation of the intervention? How is the intervention implemented in health care practice?		
Hospital level & Patient level		
Inhibiting and promoting factors	Document analysis	Transition and intervention phases
Hospital level		
Implementation status, e.g.: - Status of technical implementation - Status of implementation of TOP processes	Document analysis	Transition and intervention phases

Domain – Recruitment: Who receives the intervention?		
Hospital level		
Data on representativeness, e.g.: - Structural variables of alternative hospitals	Data extraction with survey form	Control phase
Participation information, e.g.: - Reason for participation - Implementation policy and practices, resources - Tension for change, public needs (CFIR)	Interview: key person at the hospital (e.g. management, project manager)	Transition phase
Patient level		
Data on the recruitment process, e.g.: - Number of consents	Document analysis	Control, transition and intervention phases
Domain – Implementation: Is the intervention implemented and applied in principle, as planned? To what extent is the intervention implemented and applied?		
Hospital level		
Implementation process and implementation outcomes, e.g.: - Appropriateness, feasibility, acceptability	Written survey: pharmaceutical and medical staff	Intervention phase
- Implementation of intervention according to standard, adaptations to the interventions - Fidelity, dose, reach	Document analysis	Transition and intervention phases
Patient level		
Implementation process and implementation outcomes, e.g.: - Perception and evaluation of intervention components such as contact with pharmacist - Reach, dose	Written survey: enrolled patients	Shortly after discharge (t0) and approximately 90 days after discharge (t1)
	Document analysis (software data)	Intervention phase

Domain – Mechanisms of impact: How is the intervention accepted by those involved? What are the unintended consequences and how are they to be evaluated?		
Hospital level **Response, e.g.:** - Intervention evaluation and attitudes towards TOP intervention - Interprofessional collaboration - Use of intervention in work routine (normalisation process)	Interview and written survey: pharmaceutical and medical staff Document analysis (software data)	Intervention phase Intervention phase
Patient level **Response, e.g.:** - Attitudes to and experiences of TOP intervention	Interview: subsample of enrolled patients	After discharge from hospital, Intervention phase
Domain – Effectiveness: How effective is the intervention, as perceived by the participants? How are the results to be interpreted in relation to the targeted outcome parameters (primary and secondary outcomes)?		
Hospital level **Sustainability, e.g.:** - Organisation-related expectations of the intervention met - Intentions for continuation	Interview: key person at the hospital (e.g. management, project manager)	Intervention phase/follow-up phase
Reflection of the implementation process	Interview: inter-hospital group of experts	Intervention phase/follow-up phase

Transsektorale Optimierung der Patienten-sicherheit

Information for patients on participation in the project "Trans-sectoral optimisation of patient safety" (TOP)

Dear Patient,
We would like to provide you with this information for patients about the TOP project, which aims to improve the safety of medication therapy during a hospital stay and avoid adverse drug reactions, and encourage you to participate in the project.

What is the aim of the project?
When you are admitted to hospital there is often insufficient information available about your current medication and your medical history. In addition, hospital pharmacists rarely support the treating physicians in the treatment of patients in hospitals.
In the TOP project everyone works closely together to identify medication errors and avoid adverse drug reactions. With the help of specially developed software, hospital pharmacists check your medication and regularly exchange information for optimal medication therapy with your hospital doctors. In particular, patients who suffer from several illnesses and are taking several medications at the same time will benefit from this project. In this way, patients who have a particularly high risk of drug interactions due to their previous history or their current medication are also identified in time. They are monitored particularly closely by the hospital pharmacists.
Another new feature is that hospitals can now obtain information about your medical history from your statutory health insurance to help them plan and provide optimum care for your medication. For this purpose, participating hospitals are connected to the computer data centre commissioned by your statutory health insurance via a technical network. Using the software, hospitals receive information at short notice about which medicines, therapeutic aids and appliances have been prescribed to you in the last 3 years and which diagnoses and treatments are documented, as well as information about co-treating physicians and therapists. Additionally, the exchange with your general practitioner is ensured by structured discharge management in this project.

You can find further information in the "Information for patients on the processing of personal data".

Scientific evaluation
The TOP project is scientifically monitored and evaluated by the University of Wuppertal in cooperation with the University of Bielefeld and the University of Cologne. As part of the evaluation, the scientists check whether the new measures can prevent damage to health.
Scientific evaluation is carried out on the basis of data on your medical history and prescribed medications provided by your statutory health insurance and the data documented in the software. Surveys and interviews are another elementary component of the evaluation, because your personal experiences are of particular importance to us. Those data will be collected after your hospital stay. If you have agreed to be contacted by post, the questionnaires will be sent to you by your statutory health insurance. Further information on data collection for the evaluation is attached to this questionnaire.

How can I participate in the project?

After receiving detailed information about the project and the procedure, you state your willingness to participate in the project by signing the statement of participation and declaration of consent. This statement is also valid for further stays in the same hospital until the end of the project.
Participation begins on the day of signing. With your signature, you authorize the hospital to collect data on your medical history held by your statutory health insurance to check your medication therapy. Participation in the TOP project is voluntary and free of charge. There will be no disadvantages for you if you decide not to participate.

Can I end my participation in the TOP project?
Your participation ends automatically when your insurance relationship with your statutory health insurance ends or when the project ends. Your agreement to participate can be withdrawn at any time; you do not need to give any reasons for doing so, and this will not have any negative effects on your medical treatment. You only need to state in wirting that you wish to cancel your participation and send the cancellation letter to your statutory health insurance.
However, your withdrawal only takes effects from the time you declare it. It has no retroactive effect. The processing of your data up to that point in time remains lawful.

Information for patients on the processing of personal data (TOP) (abbreviated version)

First things first: BARMER, AOK Nordost, their contractual partners and the service providers involved are very conscientious about data protection.

Your personal data is processed on the basis of sections 63, 284 and 295a of Book V of the Social Code as well as the statement of consent to data processing given by you. As part of your participation in the TOP project, a variety of data and information collected from you and about your treatment is stored and processed:

Participation data
Your signed statement of participation and consent will be archived by the hospital in your medical records. In addition, your participation will be documented by your statutory health insurance in your electronic patient file.

Data on medical documentation
The hospitals participating in the project collect medical data from you as part of your inpatient treatment. This data is part of standard medical documentation. The documentation on your current treatment is stored on the hospital server. Your statutory health insurance has no access to the patient data generated at the hospital.

Data in connection with past treatments and prescriptions
As part of your participation in the TOP project, your statutory health insurance will provide the hospital with all the information about your medical history in the past 3 years that is necessary and important for your treatment. It will provide this information digitally using special software. By signing the statement of participation and declaration of consent, you agree that participating hospitals may view the data on your medical history held by your statutory health insurance as soon as you have signed the statement.

Use of software
The TOP project uses special software which transmits the health insurance data to the hospitals in encrypted form. This software also documents your current treatment data and medications. Only authorised hospital employees have access to the software and to your data. The hospital will access the software over a specially secured data connection from the hospital to the data centre of your statutory health insurance. At the end of the project or when a hospital leaves the project, the hospital`s access rights to your data will be blocked by your statutory health insurance.

Information for general practitioners on current prescriptions
In your general discharge documents, your referring doctors receive therapy recommendations for your further treatment. In addition to the current national medication plan, they will also receive information on whether and why the medication has been changed.

Scientific monitoring and evaluation without disclosure of your name
The University of Wuppertal in cooperation with the University of Bielefeld and University of Cologne will evaluate the medical data related to your personal treatment. This concerns data collected during your hospital stay, information documented in the software, and data from your statutory health insurance. In addition, data is collected via surveys and interviews. All this data will be linked together during scientific evaluation. The universities commissioned with this evaluation will only be provided with your personal data once it has been pseudonymised. This means that your name and other identifiers (e.g. insurance number) are replaced by labels. Therefore, it will not be possible to make inferences about your identity.

Data protection and data processing
Your personal data will be used only to carry out the contractual tasks of the project. The collection, processing and use of data are governed by applicable provisions on the protection of social data according to the German Social Code and on the protection of personal data in accordance with the General Data Protection Regulation (GDPR)) and, if applicable, the Federal Data Protection Act as amended from time to time. Your statutory health insurance and its project partners are obliged to comply with all data protection regulations. This also applies after your treatment ends.

Data storage at your statutory health insurance & at the hospital
Your participation data collected during the project and stored by your statutory health insurance will be deleted in accordance with statutory provisions when you leave this project, to the extent that they are no longer required for complying with statutory provisions, and otherwise no later than10 years after the end of your participation. At the end of the project or when a hospital leaves the project, the access rights of participating hospitals to patient-related data on their medical history will be blocked at your statutory health insurance.

Consent and revocation of consent to data processing
The data processing described is only permitted if you have consented to such processing. Your statement of consent forms part of your statement of participation. Without your consent, participation in the project is not possible. You can withdraw your statement of participation and declaration of consent at any time by writing your statutory health insurance; you do not need to give reasons. Further information can be found in "Information for patients on participation".

Transsektorale Optimierung der Patienten-sicherheit

Statutory health insurance		
Name of the insured person		Date of birth
Cost unit identifier	Insured person number	Status
Registration number of healthcare institutions	Physician identifier	Date

QR-Code

DECLARATION OF CONSENT AND STATEMENT OF PARTICIPATION IN THE PROJECT: "TRANS-SECTORAL OPTIMISATION OF PATIENT SAFETY"

1. Statement of participation:

I hereby declare that
- I would like to participate in the TOP project.
- I have received detailed and understandable information about the contents and objectives of the project and the processing of my data that will be required to carry out the project. I have had sufficient opportunity to discuss the implementation of the project. All my questions were answered satisfactorily.
- I have received, read and understood the "Information for patients on participation" and the "Information for patients on data processing".
- I am aware that my participation in the project is voluntary.
- I am also aware that my participation in the project begins with the signing of this participation and consent form. My participation will end if I withdraw this statement, when the project ends or I am no longer insured with BARMER.

Cancellation policy
I can withdraw my statement of participation in writing, without giving reasons, at any time. I will not suffer any disadvantages.
By post:
E-mail:

. . _____

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

2. Declaration of consent

I have received the “Information for patients on participation” and the “Information for patients on data processing” and have taken note of them. I consent to the collection, processing and storage of my personal data as described and required for the project.

I agree that:

- The hospital will transmit my participation data (name, date of birth, insurance number and start of participation) electronically to my statutory health insurance provider.
- During my hospital stay, the hospital may retrieve data on my treatments and prescriptions in the past 3 years from my statutory health insurance. Details are described in the "Information for patients" provided to me. I am aware that the data will be retrieved at any time after my signature. On the basis of this data hospital pharmacists will carry out a detailed review of my medication therapy.
- Upon discharge, the hospital will provide the referring doctors with a therapy recommendation for further medication and, if necessary, contact them for a personal discussion.
- My signed statement of participation and declaration of consent will be stored in my patient file at the hospital and my statement of participation is documented in the software. My statutory health insurance will store my participation data (start of participation, hospital) in the electronic insurance file (eFile).
- My data will be treated confidentially by the hospital and by my statutory health insurance in compliance with applicable data protection regulations.
- My health insurance data will be processed for the purposes of scientific analysis (evaluation) by the scientific institutes involved in the project. My medication data may be retrieved from the database held by my statutory health insurance for checking against the criteria for participation in the project and for the scientific evaluation. Pseudonymised means that my name and other identifiers (e.g. insurance number) will be replaced by labels that rule out me being identified.
- My statutory health insurance provider may send me survey questionnaires by post to evaluate the project.

I acknowledge that

- In the context of this project, personal data will be processed in a way that goes beyond the usual scope of medical treatment - but which is important for the success of the project.
- My data will be processed by the hospital, my statutory health insurance and the evaluation team in compliance with applicable data protection regulations.

Cancellation policy
I can withdraw my statement of participation in writing without giving reasons, at any time. I will not suffer any disadvantages.
By post:
E-mail:

. . _____

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

Information for patients on the scientific monitoring and evaluation of the project *„Trans-sectoral optimisation of patient safety“* (TOP)

Dear Sir or Madam,
We would like to ask you whether you would like to take part in the data collection (surveys, telephone interviews, document analysis, analysis of claims data) being carried out by the University of Wuppertal together with the University of Bielefeld and the University of Cologne. The data collection is part of the scientific monitoring of the project "Trans-sectoral Optimisation of Patient Safety - TOP", which was initiated by BARMER.

Please read the evaluation information carefully and ask questions if you do not understand something.

Medication therapy is an essential component of the medical treatment of patients. In hospitals, several parties are involved in the process of medication treatment from admission to discharge. Inadequate information transfer or coordination between hospital staff and general practitioners (GPs) can have various consequences for patients. For example, there is a risk of drug interactions occurring or the patient may be hospitalised again.By implementing a new form of care, the aim is to achieve intensified and therefore improved pharmaceutical care for patients. The medication process in hospital will be supported electronically from admission to inpatient treatment through to discharge. The aim is to avoid interactions and unnecessary hospitalisation and to improve quality of life.

With your support, we would like to analyse the effects of this new form of care. This will examinewhether an improvement in the medication management of hospitalized patients can be achieved.

What is the evaluation process and what data do we need?
The evaluation will run from August 2021 to May 2024, during which time the new form of care will be introduced in your hospital (by mid-2023 at the latest) alongside the normal form of care. The implementation of the new form of care will result in changes to hospital processes. It may therefore not be visible to you whether the new form of care has already been introduced in your hospital. Whether and to what extent the new form of care is implemented at the time of your stay in the hospital treating you will be decided at random.

If you have decided to participate in the project and the evaluation, you will receive **two questionnaires over a period of three months**. The questionnaires will be sent to you by post by your statutory health insurance provider (SHIP). Depending on when and in which department you were hospitalised, an employee of the University of Wuppertal will also contact **you by telephone** once after **your hospital discharge**.. In addition to the questionnaires and the telephone interview, project staff will gain **insight into your discharge documents.**

What happens to your data (data protection information)?
All information and statements that you provide in the written questionnaires and the information from the discharge documents are collected in pseudonymised form. Pseudonymisation means that your name and other identifiers (e.g. insurance number) are replaced by labels. Therefore, it will not be possible to make inferences about your identity.An identification list, which makes direct personal reference possible, is managed by project staff of SHIPs and kept under lock and key. These persons are bound to secrecy. In a further step, the pseudonymised data from the written surveys is linked to your pseudonymised claims data of SHIPs. The purpose of the link is to combine the data of the same person for scientific analysis. The data is linked using an encryption procedure and is carried out by an independent trust centre. The project team of the universities involved in the evaluation will be granted access to the linked data set for scientific analysis. In addition, your contact details (name, telephone number) may have been collected by the hospital project team during your hospital stay. After your consent to the scientific monitoring and evaluation, this information will be forwarded to the project team at the University of Wuppertal, who may contact you to arrange an appointment for the telephone interview.The telephone interview is recorded using a tape recorder and then transcribed. All information is anonymised, i.e. names, places and other personal details are changed so that it is no longer possible to draw conclusions about individual persons. The personal data (name, telephone number) will be stored separately from your survey and health data at the University of Wuppertal and will be completely deleted after the end of the research project. This ensures that the data is anonymised after the end of the project.

We assure you that all persons involved will comply with the data protection laws. The legal basis for the processing of the data is in accordance with the General Data Protection Regulation (GDPR).

Who can I contact if I have any questions?
The University of Wuppertal will be happy to answer your questions at any time.

Consent and revocation of consent
Participation in the evaluation is voluntary. If you agree to participate, please confirm your consent by signing the enclosed form (Declaration of consent for scientific monitoring and evaluation). You can revoke your declaration of consent at any time in writing without giving reasons and without any disadvantage to you. If you withdraw your consent, no further data will be collected. The data already collected and processed up to the time of your revocation will be anonymised and can therefore no longer be attributed to you personally. Your personal data (e.g. name, telephone number) will be deleted together with your entry in the identification list.

Declaration of consent for patients for scientific monitoring and evaluation of the project *Trans-sectoral optimisation of patient safety* - TOP

I have been sufficiently informed about the contents of the evaluation and its procedure. I have read the enclosed "Information for patients on scientific monitoring and evaluation". I have had the opportunity to ask questions and have received satisfactory and complete answers. I have had sufficient time to decide to participate in the evaluation and realise that participation is voluntary. I am aware that my data will be processed pseudonymised. The withdrawal of consent does not affect the lawfulness of processing based on consent before its withdrawal. In the event of revocation, no further data will be collected. In this case, I can arrange for the data to be deleted.

I am aware that personal data about me, as described in the attached "Information for patients on scientific monitoring and evaluation", will be collected and recorded at the University of Wuppertal.

I agree that the data will be stored for at least 10 years after completion or discontinuation of the study and subsequently only archived in anonymised form (without personal reference).

Changes to the evaluation data (e.g. correction or deletion of individual details) are possible until the time of anonymisation (after the evaluation has ended). I know that I can withdraw my consent to participate in the evaluation at any time and without giving reasons, without any disadvantages for my further medical care. If I withdraw my participation, I can request the deletion of all data collected to date that has not been anonymised. To have the data deleted, please get in touch with the contact person at the University of Wuppertal..

I have been informed about my data protection rights. I agree to the collection, processing, storage and transmission of the data in pseudonymised form. I also agree that my pseudonymised data from the written survey may be linked to my pseudonymised claims data of SHIP and I also agree that if an employee of the hospital has recorded my contact details (name and telephone number) during my inpatient stay in order to organise the telephone interview, these will be forwarded to the University of Wuppertal.

I will not incur any costs or other obligations by participating in the evaluation. I have received a copy of the information sheet and this declaration of consent.

I hereby declare my voluntary participation in this evaluation. At the same time, I give my consent for the project team to conduct the surveys and interviews and to inspect my discharge documents. I also agree that my data from the written survey may be linked with my pseudonymised claims data of SHIP and, if applicable, with the medication data of the hospital for the scientific evaluation using an encryption procedure.

Participant:

Surname, first name *(block capitals)*	***Place and date*** *(to be filled in personally)*	***Signature***

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Implementation of an electronic medication management support system in hospitalised polypharmacy patients: study protocol of a stepped-wedge cluster-randomised controlled trial (TOP study)

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TITLE

Implementation of an electronic medication management support system in hospitalised polypharmacy patients: study protocol of a stepped-wedge cluster-randomised controlled trial (TOP study)

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TOP study group

ABSTRACT

Introduction: Polypharmacy is associated with an increased risk of adverse patient outcomes across various settings, including inpatient care. To enhance the appropriateness of medication therapy management for patients during hospital stays, computerised interventions have shown promise with regard to patient safety. This study assesses whether the implementation of a clinical decision support system will optimise the process of inpatient medication therapy to prevent inappropriate medication use and thus promote patient safety.

Methods and analysis: The intervention will be evaluated in a prospective, cluster-randomised controlled trial using a stepped-wedge design. The study will be conducted in 12 hospitals across Germany over a total period of 33 months. Patients will be treated according to the group status of the hospital and receive either standard care or the TOP intervention. The primary outcome is the combined endpoint of all-cause mortality and all-cause hospitalisation. Secondary endpoints are e.g. inappropriate prescriptions, utilisation of different health services, cost-effectiveness, as well as patient-reported outcome measures. Parameters describing the attitudes of patients and healthcare professionals towards the intervention and organisational change processes will be collected as part of the process evaluation. The primary endpoint will be evaluated using hospital and outpatient claims data from participating statutory health insurances at the population level. There are multiple secondary endpoints with data linkage of primary and secondary data at study participant level. Statistical analysis will make use of (generalised) linear mixed models or generalised estimating equations, taking account of independent covariables. All data analyses of the process evaluation will be descriptive and explorative.

Ethics and dissemination: Data collection, storage and evaluation meet all applicable data protection regulations. The trial has been approved by the Ethics Committees of the University of Wuppertal and the Medical Association of Saarland, Germany. Results will be disseminated through workshops, peer-reviewed publications, and local and international conferences.

Registration: DRKS00025485

Keywords

Patient safety, Medication Therapy Management, hospitals, clinical decision support systems, polypharmacy, evaluation/outcome and process assessment, stepped-wedge design, randomised controlled trial

ARTICLE SUMMARY

Strengths and limitations of this study:

- The TOP study is a cluster-randomised controlled trial in a stepped-wedge design that will provide evidence on the effects of a clinical decision support system (CDSS)-based intervention for medication management in inpatient care on patient-relevant outcomes.
- We hope to gain extensive insights into the effects by using different linked data sources; in particular, claims data from two statutory health insurance providers (SHIPs), self-reported patient data, and CDSS software data.
- In addition, the study will conduct a comprehensive process evaluation to provide insights into the implementation process, barriers to and factors facilitating implementation, and embedding activities in routine care.
- Due to convenience sampling at hospital level, it may be that the hospitals participating in the study are already more receptive to medication therapy management (MTM) and aware of the technical possibilities for its realisation compared to other hospitals in Germany.
- Since some hospitals have already established programmes for MTM, they start with better preconditions than others, potentially influencing various study endpoints; the comparability of study groups will be addressed by (1) collecting data on the primary endpoint from a pre-observational period and (2) collecting information on established measures in the hospital, allowing for the development and utilisation of appropriate control variables in the analysis.

INTRODUCTION

Polypharmacy, mostly defined as the concurrent use of at least five medications daily [1], is associated with an increased risk of adverse outcomes, including mortality, hospitalisation, adverse drug reactions, drug-drug interactions, medication non-adherence, and high health care costs [1-6].

The pooled prevalence of polypharmacy across various healthcare settings, regions, and all medication classes is estimated at 37% [3], with a slightly lower estimate of 30% reported for Germany [4]. This prevalence varies not only between countries and different healthcare settings, but also between population age groups. The prevalence of polypharmacy is in addition higher in inpatient settings compared with outpatient and community settings [3, 4, 7].

During transition from outpatient to inpatient care, there are often information gaps, potentially leading to avoidable harm. Adequate and safe decisions on diagnostics and therapy in hospital require

full knowledge of a patient`s medical history and the outpatient treatment received [8-10]. In addition, prescription errors are often not recognised on admission to hospital, and medication errors in hospitals occur frequently [11-15]. Besides these, an inadequate transfer of information or inadequate coordination between different care providers after discharge from hospital can also lead to complications [9, 16]. Overall, hospitalisation is associated with an increased risk for patients' medication safety [8, 9, 17].

To enhance the appropriateness of medication therapy management (MTM) during hospital stays, computerised interventions have shown promise with regard to patient safety. Clinical decision support systems (CDSS), as one of the IT-based interventions, are recognised as a promising approach to improve process-related outcomes such as, e.g. prescription, drug-drug interaction. However, there is limited evidence of the effects on patient-level outcomes such as readmission and mortality [18-24].

The TOP study ("*Transsektorale Optimierung der Patientensicherheit*" or "trans-sectoral optimisation of patient safety") will implement a complex CDSS-based intervention to optimise the process of inpatient medication therapy at admission, during the patients' stay in hospital, and at discharge, to prevent inappropriate medication use and thus promote patient safety. The term 'complex intervention' refers to the characteristics of the intervention itself (e.g. different actors involved in the delivery and implementation of this multi-component intervention). Complexity may also arises in our study from the interaction of the intervention with its context and the steps that need to be taken to implement the intervention [25].

OBJECTIVES

The primary objective of TOP is to optimise the process of medication therapy for inpatients at admission, during the patients' stay in hospital, and at discharge, in order to improve MTM and to achieve related outcomes such as a cross-sectoral improvement in quality, safety, cost-effectiveness and coordination of medication therapy, as well as increasing patient autonomy and self-management skills for inpatients with polypharmacy. We will demonstrate whether this complex intervention can contribute to an improvement of care within a prospective, cluster-randomised controlled trial (C-RCT) and using the example of the statutory health insurance system in Germany.

Therefore, the TOP trial aims to:

1. Evaluate the effectiveness of the complex intervention: we will examine whether the intervention reduces mortality and readmissions in polypharmacy patients treated in hospital. Furthermore, we intend to assess the impact of the intervention on inappropriate prescriptions, and severe and avoidable adverse drug events, as well as the utilisation of outpatient emergency care.

2. Evaluate the cost-effectiveness of the intervention: we will determine incremental cost effectiveness ratios (ICER); in particular, the cost per avoided hospitalisation and/or death and the cost per quality-adjusted life year from a payer's perspective.
3. Evaluate patient-reported outcome measures (PROs) such as health-related quality of life, and patient-reported experience measures (PREMs) such as experienced continuity of (pharmaceutical) care and patient satisfaction with information about medication. These measures will be collected to complement the claims data-based assessment of effectiveness from the patient's perspective.
4. Conduct a socio-economic impact assessment to support sustainability planning for spreading and scaling up the TOP intervention.
5. Evaluate the implementation process and its outcomes in participating hospitals and assess factors hindering and facilitating the implementation of digital interventions.

METHODS

This study protocol was written in accordance with the SPIRIT reporting checklist [26] (online supplementary material, file 1).

Study design

The intervention will be evaluated in a prospective, cluster-randomised controlled trial (C-RCT) using a stepped-wedge design (SWD) with an observation period of 33 months (30 months for recruiting + 3 months` follow-up of the last patient to be included) running from August 2021 to April 2024. The trial is designed as a hybrid type-1 effectiveness-implementation study addressing, besides effectiveness as the primary focus, the implementation of the TOP intervention as well [27]. A total of 12 hospitals will be randomly assigned to three clusters. Each cluster starts in a control phase. The intervention will then be introduced to each cluster with a time delay (i.e. in steps), similar to a unidirectional cross-over design (see Figure 1). The patients will be treated according to the group status of the hospital and, depending on that group status, receive either standard care (control phase) or the TOP intervention (transition and intervention phase). The study design allows the recording and comparison of temporal effects as well as an intensive process evaluation.

The intervention represents a novel process currently undergoing untested implementation within the hospital setting. Therefore, two hospitals accompanying the study are responsible for testing and optimising the acceptability, appropriateness and feasibility of the intervention and its implementation. In addition, these test hospitals play a crucial support role for the hospitals involved in the C-RCT, helping them to successfully implement and embed the TOP intervention.

Setting and trial population

Study setting

The study will be carried out in 12 hospitals across Germany. These will include hospitals in different states, of different sizes, with different ownership structures, and with departments relevant to the study (see Inclusion criteria). Each participating institution must give its consent by signing a cooperation agreement.

Inclusion and exclusion criteria

Hospital level

Hospitals can participate in the study if they are willing to hire a pharmacist for the duration of the study or to assign the study tasks to a suitably qualified member of staff. Furthermore, the hospital should be willing to assign staff to study-related tasks, such as informing and enrolling patients willing to participate, for the duration of the C-RCT. Hospitals that are already participating in a similar project will be excluded.

Staff level

Healthcare professionals (HCPs): The HCPs in the study will be pharmacists (ward or hospital pharmacists, depending on the existing structure of the hospital) and physicians from the participating departments who are directly or indirectly involved in the TOP intervention. Additionally, each participating hospital provides key persons (e.g. project manager at the hospital, head of pharmacy and of the specialised department) as a responsible key informant on the implementation process.

Patient level

Included in the trial will be all patients aged 18 years and over and insured with participating health insurance providers (BARMER and AOK Nordost) who take at least five prescribed drugs and were initially hospitalised in a participating hospital's department of internal medicine, geriatrics, visceral surgery, vascular surgery, cardiac and thoracic surgery, orthopaedics and trauma surgery, neurology, or urology during the study period. Inclusion in the study will be consecutive. Patients undergoing oncological treatment will be excluded due to regular hospitalisation based on treatment cycles.

Recruitment

Hospital level

Hospitals are recruited nationwide, the aim being to recruit hospitals from several states, of varying size and, if possible, having the departments relevant to the study. The hospitals participating in the trial are based on a convenience sample.

Staff level

At the beginning of the trial, hospitals will designate key informants, who will be invited to participate in the data collection of key persons. In order to survey all HCPs (complete enumeration), medical and

pharmaceutical staff will be recruited via key persons in the organisation concerned. They will also hand out the survey documents. Before taking part in data collection, all persons will receive written information about the surveys.

Patient level

Patients will be recruited at participating hospitals and will receive either standard care (control phase) or the TOP intervention (transition or intervention phase), depending on the hospital's study phase. All patients who meet the inclusion criteria will be invited to participate in the TOP study by pharmacists during their admission as an inpatient. Patients will be provided with written information and must give their consent in order to participate in the study. Although patient recruitment in the hospitals started in August 2021 (month 1), participant enrolment did not start until November 2021. The start was delayed (compared to the start of the C-RCT) because the recruitment process and the transfer of patient information to the SHIPs had to be introduced and established in the study hospitals, and the processes for checking patients' inclusion criteria and sending study documents to patients by the SHIPs had to be adapted. This had to be based on the existing structures and processes of healthcare practice and could therefore only be tested and adapted after the start of the C-RCT. The recruitment period ends on the last day of the intervention phase for all hospitals (month 30).

Randomisation

Randomisation takes place at the hospital level, i.e. at the start of the project, all participating hospitals are randomly assigned to a cluster. Randomisation will be stratified based on the hospitals' size (determined by number of beds and cases) to ensure that the numbers of control and intervention patients are balanced. There will be no randomisation at patient level, as it is assumed that the service providers in the hospitals will experience learning effects, which would then influence the treatment of patients from the control group.

Intervention and control

Description of the intervention

The TOP intervention is a complex intervention that focuses on intensified pharmaceutical care for patients on admission to hospital, during their inpatient stay, and on discharge. MTM is a key component of the intervention and will be carried out electronically using CDSS-based software. The use of claims data from participating SHIPs, such as diagnosis, medication and healthcare service utilisation, facilitates the generation of CDSS insights, with additional parameter values such as renal function and body weight, along with dosage information and over-the-counter medication information, being entered by a pharmacist or physician. A physician's confirmation of current prescriptions in the CDSS is also required to prevent outdated prescription data from being included in the medication review. Following the medical history, the CDSS evaluates the medication and generates alerts in three domains (drug-related, dose-related and drug-therapy related). The

generated alerts are presented in a hierarchical order of severity, ranging from most serious to least serious, and are categorised as 'Red', 'Yellow', 'Grey', or 'Info'. The formulation of these warnings is informed by scientific and regulatory publications, as well as drug commissions. The process is carried out by pharmaceutical and medical professionals employed by the TOP- technology partner, using the WHO UMO algorithm [28] and the criteria defined by the Drug Interaction Probability Scale [29]. A detailed description of the several interdependent components of the intervention based on the TIDieR Checklist [30] is given in Table 1, Components of TOP intervention (online supplementary material, file 2).

Implementation of the intervention

The intervention will be implemented in a time-lagged design in participating hospitals. Over the course of the study, each hospital will pass through the control period, the transition period, and the intervention period. In the control phase, hospitals provide the usual care and initiate preparations for the intervention use such as establishing technical connections or hiring required staff. The intervention is introduced in the hospitals for the first time during the transition phase. During this period the intervention is tested under everyday conditions of the hospital. It is possible to make procedural adjustments to adapt the use of the intervention to the specific structures and processes of the respective facility. This transition period is followed by the intervention period, in which the intervention will be fully realised under everyday conditions. For validating effectiveness, it is crucial that certain actions of implementation are realised in the appropriate period and completed before transitioning into the next period.

Multicomponent implementation strategies will be carried out to enhance the implementation process and the outcomes (e.g. fidelity) of the TOP intervention in routine care. The initial implementation strategies in TOP cover the elements of providing interactive assistance, developing stakeholder interrelationships, training and educating stakeholders, engaging consumers, utilising financial strategies, adapting and tailoring the TOP intervention to the context, and using evaluative and iterative strategies based on the Pragmatic Implementation Strategy Reporting Tool [31]. For details of the implementation strategies, see Table 2 Implementation strategies of TOP (online supplementary material, file 3).

Control group

In the control phase, hospitals provide care according to their current standards. As we do not explicitly include MTM naive hospitals, it cannot be ruled out that hospitals may provide MTM or use CDSS if they have already established these elements as part of their standard care process.

Outcome assessment

Primary outcome

The primary outcome, based on claims data from participating SHIPs is the combined endpoint of all-cause mortality and all-cause hospitalisation in polypharmacy patients three months after discharge.

Secondary outcomes

The primary endpoint is followed by several secondary endpoints regarded as significant for the overall success of the intervention. In detail, these include the effectiveness and cost-effectiveness of the intervention regarding the following aspects:

1. Percentage/proportion of patients who receive inappropriate prescriptions and percentage/proportion of patients who suffer from severe and avoidable adverse drug events at the hospital or within three months post-discharge (based on claims data).
2. Utilisation of different health services such as emergency care (based on claims data).
3. Cost-effectiveness and cost-utility of the intervention compared to standard care (based on claims data and survey data).
4. Patient-reported outcome and experience measures (PROMs and PREMs) will be collected by questionnaire at two measurement points: shortly after discharge from hospital (t0) and approximately 90 days after discharge (t1). PROMs and PREMs will include adverse drug events (PRO-CTCAE™ [32]; t0 & t1), experienced continuity of (pharmaceutical) care (Patient Continuity of Care Questionnaire [33]; t0 & t1)), satisfaction with information about medicines (SIMS-D [34]; t0 & t1), adherence (MARS [35]; t0 & t1), patient enablement/empowerment (Generic Questionnaire for Measuring Patient Enablement [36]; t0 & t1), patient safety (Patients' Perceptions of Safety Culture Scale [37]; t0) and health-related quality of life (VR-6D and EQ-5D-5L [38, 39]; t0 & t1).
5. Costs and benefits (financial, resources/time, intangible) of the intervention at the level of stakeholders and the service overall (based on claims data, software routine data, survey data).

Process evaluation

A process evaluation will be conducted to understand the intervention effects of complex interventions such as TOP and to identify their potential for generalisability and possible improvement [40]. The process evaluation will therefore involve the scientific monitoring of the intervention throughout the duration of the planned C-RCT and address questions of a process-descriptive (e.g. How is the intervention implemented in health care practice? What factors inhibit or promote implementation of the intervention?) or organisational-change nature (e.g. How the intervention influences the structure, workflow, or culture within the participating hospitals?). The process evaluation will assess how and why the intervention works (or doesn't work) in the specific context where it is being applied. The evaluation will follow the Medical Research Council's recommendations

for process evaluations of complex interventions [41], be guided by the framework established by Grant et al. [42] for monitoring cluster-randomised controlled trials, identify effect-modifying factors, and focus on exploring mechanisms of impact. The process evaluation of TOP will include different data collection methods (written questionnaires, interviews, document analysis of field notes and software data) from different target groups (patients, pharmaceutical and medical staff, key person at the hospital e.g. management, project manager). Data will be collected on context (e.g. Organisational Readiness for Implementing Change, pharmaceutical and medical staff acceptance and use of the technology, previous MTM experience of patients), recruitment (e.g. reasons for participation, implementation practices and resources of hospitals, number of patient consents), implementation (e.g. appropriateness, feasibility and acceptability of the intervention by pharmaceutical and medical staff, perception and evaluation of intervention components by enrolled patients, such as contact with the pharmacist), mechanism of impact (e.g. use of intervention in work routine, patients' attitudes and experiences of the TOP intervention), and effectiveness (e.g. organisational expectations of the intervention met, hospitals' intentions to continue with the intervention) throughout the duration of the C-RCT. The data collection time points at the organisational level will be determined by the hospital's affiliation with one of the three switching cohorts. More detailed information on the data collection of process evaluation is given in Table 3, Data collection of process evaluation (online supplementary material, file 4).

Data collection and management

Data collection

Secondary data/claims data from participating health insurance providers

Claims/routine data from August 2021 to April 2024 will be used in the analysis. Data collection is therefore longitudinal and data will be available for the duration of the C-RCT, as well as the pre-observation period so as to establish a baseline for the primary endpoint.

The required claims data from participating SHIPs providers are specified in a coordinated minimal data set. Variables included in the dataset are sociodemographic patient data (sex, age, insurance status, reason insurance coverage ended), outpatient diagnoses and outpatient services (ICD-10 diagnoses, services according to the physician’s fee scale), medication (pharmaceutical registration number, ATC code, duration of the therapy (DDD), costs), inpatient data (start and end date of each hospitalisation, admission and discharge diagnoses, secondary diagnoses, operation and treatment procedures, costs), long-term nursing care (start and end date, level and place of care, costs and type of service), incapacitation for work (ICD-10, start and end, costs), ambulance services (start and end).

Primary data

Primary data will be collected from patients treated with the intervention (transition and intervention phase) as well as those who have confirmed their willingness to participate in the data collection (control phase) and are able to consent. Data will be collected through a questionnaire sent by post, shortly after discharge from hospital (t0) and approximately 90 days after discharge (t1). All survey participants who have agreed to be contacted by the health insurers after hospitalisation and who meet the inclusion criteria of the survey will be contacted. This procedure was chosen to ultimately achieve a response rate of at least 25% of all study patients. The questionnaires will be delivered by the health insurance providers and will be returned to the University of Wuppertal. Once the pseudonymised questionnaires arrive at the University of Wuppertal, they will be scanned in.

To monitor implementation status and possible obstacles to the implementation of the intervention, the hospitals will be asked to report any unexpected events every 3 months. These are events at the individual level (e.g. illness of the staff responsible), ward level (e.g. staff shortages) and hospital level (e.g. strike). The survey will be sent to the contact persons in the hospitals via e-mail.

Data from the software solution

For the data from the software solution for evaluating the secondary endpoints (medication plans) and user behaviour (process evaluation), an MDS is coordinated with the operator of the software, enabling the corresponding evaluations. Data from the software solution include e.g. information about boxes clicked within the software by the pharmacists, such as “Medication therapy recommendation set”, “Pharmaceutical discharge interview done”, “Printed handout on medication therapy given to patient“, the medication the patients take, interactions, and alerts.

Data from process evaluation

The collection process for the data from process evaluation will depend on the type of data collection. Qualitative data will be collected through face-to-face or telephone interviews from a subsample. A structured guide will be used during the interviews. All interviews will be recorded and subsequently transcribed according to appropriate guidelines [43]. In the case of written surveys of staff (medical, pharmaceutical), the aim is to conduct a full survey. The questionnaires will be created using Teleform® and sent to the healthcare professionals by the responsible evaluation partner (BUW). Delivery of questionnaires to patients (T0 and T1) for collecting data for the process evaluation is identical to the data collection process for primary data. All completed questionnaires will be sent back to the responsible evaluation partner (BUW). Once received, the pseudonymised questionnaires will be scanned and digitised.

For the document analysis, field notes used during the introduction and implementation of the intervention or created during the evaluation will be collected. They may include e.g. training protocols

and hospital implementation guides. Hospitals will provide copies of documents to the responsible evaluation partner (BUW) for analysis or grant access for data extraction. The method of document analysis will help identify e.g. factors supporting or hindering the implementation process.

The data collected, including interview transcripts, questionnaire responses, and documents will be processed using established software tools commonly used in the social sciences. These tools include SPSS, R, and MAXQDA, which allow for a thorough analysis and interpretation of the data.

Data management

The evaluation consists of two study sections, with study section 1 using only claims data from participating SHIPs at the population level, and study section 2 using claims data from participating SHIPs, primary data, and medication plan data from the software used, all at the study participant level (see Figure 2).

The primary endpoint will be evaluated using claims data from the participating SHIPs at the population level (all potential patients in the hospital, intention-to-treat, study section 1). Both SHIPs will select records for the relevant observation periods in participating wards of participating hospitals, based on the inclusion criteria of a minimum age of 18 and being prescribed three or more drugs. To estimate a baseline of MTM measures, characteristics of the primary endpoint in participating hospitals will be calculated from a pre-observation period using this dataset.

The secondary endpoint is based on multiple endpoints with a linkage of primary and secondary data (individual study participant level, per-protocol, study section 2). The secondary endpoint will be divided into the analysis of patients enrolled and treated, and patients enrolled in the control phase and receiving standard care. For patients in the control phase, claims data, primary data at the individual level (patients) and primary data at the organisational level (hospital) will be linked. The linkage of the primary data at the individual level, the software data and the claims data will be done using a pseudonym for each patient. An institutional pseudonym will be assigned to the primary data at the organisational level, collected for the formative evaluation/process evaluation for matching with the hospital concerned.

Analysis

Sample size

According to a preliminary analysis based on BARMER routine data, the incidence of readmission or death within 90 days from initial hospitalisation is 32.9% (24.81% readmission <90d; mortality 2.66% in hospital, 5.43% <90d after discharge). Assuming a 15% reduction of the primary combined endpoint to 27.97%, an α-error of 0.05, and a power of 1-β=0.80, the underlying regression model yields a

sample size of 146 treated patients, or cases per hospital per time interval (quarterly period). With 12 hospitals participating over 8 quarters (30 months excluding the transition phase), the total number of patients treated is aimed to be 14,016 (7,300 for the control phase and 6,716 for the intervention phase). An expected dropout rate of 40% increases the sample size to 23,328, with 243 patients to be recruited per hospital per quarter. To evaluate the implementation appropriately in the process evaluation, an additional 5,832 patients should be recruited for the transition phase in the 12 hospitals. This sample size was calculated using an intra-class correlation coefficient (ICC) of 0.05, which had been determined in the preliminary analysis of the BARMER data. The dropout rate is based on a previous study within the outpatient setting having a similar intervention and the same primary endpoint based on claims data from participating SHIPs [44].

Analysis of primary and secondary outcome parameters

The primary objective of this study is to determine whether this complex intervention reduces the combined endpoint of all-cause mortality and all-cause hospitalisation in adult patients with polypharmacy 90 days post-discharge.

The evaluation strategy for the primary endpoint is based on study section 1, including all patients insured with participating health insurance providers who were hospitalised in a participating hospital during the study period and fulfil the inclusion criteria. In this way, not only the effects of the intervention on patients treated with this new form of care are taken into account, but also access to the intervention and spill-over effects regarding the treatment of non-participating patients. In subordinate analysis, group comparisons will be made, in which selective contract participants are to be compared with control group patients as a subgroup.

Statistical analysis will be conducted for primary and secondary endpoints (study section 1 and study section 2) at cluster level, in the form of within-cluster and between-cluster analyses. Inappropriate prescribing is operationalised using the PRISCUS 1 list, the FORTA list and the negative drug interactions of the 'choosing wisely' (*'Klug entscheiden')* initiative. Prescriptions are available for outpatient data. Avoidable adverse drug events (ADEs) are operationalised according to Stausberg and Hasdorf [45] ICD-10 diagnoses are available for outpatient and inpatient cases. First, the primary and secondary endpoints will be analysed descriptively. The statistical analysis will use (generalised) linear mixed models ((G)LMM) [46] or generalised estimating equations (GEE) [47, 48], taking account of independent covariables (e.g. age, gender). The multilevel structure will also be accounted for by fixed time effects and random effect for clusters. The use of these statistical models enables the estimation of intervention effects through a binary covariate, where 1 represents the intervention group (clusters in the intervention period) and 0 denotes the control group (clusters in the control period). The results of the survey of unexpected events will be included in the analysis as confounders to control for

possible effects of these events. For the analysis of study section 2, medication plan data from the software will be included in addition to the confounders available in the claims data. Analyses will be adjusted for multiple testing by Bonferroni correction.

Primary patient level data analysis will be descriptive and exploratory. The statistical analysis will follow the procedures used for the routine data.

Cost-effectiveness analysis

The health economic analysis will be conducted from a third-party payer perspective, which is the perspective of the SHIPs in Germany. The incremental cost-effectiveness ratio (ICER) will be calculated by dividing the difference in costs by the difference in health benefit of the intervention compared to standard care. The analysis of all reimbursed direct health care costs will be based on health insurance claims data comprising healthcare resource utilisation regarding inpatient care, outpatient care, rehabilitative care, pharmaceuticals, therapeutic devices, non-physician specialist services, nursing (home) care, and patient transport services, and sick pay. Intervention-related costs will also be included. Benefits of the intervention will be measured by the primary outcome (hospitalisation and/or death) and the secondary outcome of health-related quality of life. Hence, the cost per avoided hospitalisation and/or death (CEA, cost-effectiveness analysis) and the cost per QALY (quality adjusted life year) (CUA, cost-utility-analysis) will be analysed.

The CEA will be based on the population level (see section data collection). However, for the CUA, data obtained by the EQ-5D-5L [39] collected in the C-RCT will be used to calculate QALYs by using the German value set [49] . Thus, the CUA will be based on a reduced sample.

Socio-economic impact assessment

In order to analyse the costs and benefits of the intervention at the level of stakeholders and the service overall, a socio-economic impact assessment (SEIA) will be conducted. SEIA is a formative evaluation to support sustainability planning of the intervention for transfer into regular care which aims to answer questions on the three levels (see Figure 3):

Methodologically, SEIA is based on cost-benefit analysis as defined by Drummond [50] and the recommendations of UK HM Treasury [51], the Federal Government Commissioner for Information Technology [52] and the White House Office for Management and Budget [53]. An already established framework and associated evaluation software developed for business model development for IT-based utility services will be used [54].

Process evaluation

All data analyses of the process evaluation will be descriptive and explorative. The analysis of qualitative data material will be either content analysis or a qualitative-descriptive analysis. In analysing the interviews, a deductive procedure will be followed initially, in which paraphrases from

the interviews are assigned to themes and sub-themes of the underlying frameworks or theories of the respective data collection (e.g. CFIR, normalisation process theory). Within the themes and sub-themes, the content will be processed inductively. The analysis of the questionnaire and software data will be descriptive and exploratory.

PATIENT AND PUBLIC INVOLVEMENT

This protocol was developed without patient or public involvement.

ETHICS AND DISSEMINATION

The TOP study was approved by the Ethics Committees of the University of Wuppertal (no. MS/AH 201028) and the Medical Association of Saarland, Germany (no. Ha 37/21). In case of important modifications of the protocol, the afore-mentioned Ethics Committees and the funding institution will be informed immediately.

Written informed consent will be obtained from the managers of each participating hospital through their signing a supply contract. Healthcare professionals will receive comprehensive information on the study before getting involved in data collection. The staff can stop data collection at any time if they wish.

Written informed consent will be obtained from all participating patients if they decide to get involved in the study during their hospital stay (individual study participant level, study section 2). A two-stage process has been developed for consent to participate in the study. Consent to participate in the study is only valid after the participant has read the information, had the possibility to ask questions and signed the informed consent for participation in the study (during the hospital stay) and the informed consent for the scientific monitoring and evaluation of the study (after the hospital stay). For model consent forms, see the online supplementary material, file 5. Any participant may withdraw their consent at any time. The data of study section 1 (claims data at the population level) are provided on the grounds that it would be unreasonable to obtain the consent of all patients insured with the participating SHIPs. These grounds include, among other things, the relevance of the study to the general population and the risk of bias due to selection effects when consent is obtained.

A declaration of consent permitting data access is a prerequisite for retrieving patient-related information from the health insurance providers. The software documents which registered user of the hospital information system has retrieved or processed information, and on which patient and at what time.

When the software is installed, a key encrypted by a fixed code and managed in the software is generated, i.e. only the software knows the patient-related data. Only authorised hospital staff can

access the data stored. Neither the health insurance nor the software provider can view the treatment data.

BARMER and the hospitals accompanying the study will be responsible for monitoring the trial, and in particular for recruiting hospitals and supporting patient recruitment and the implementation of the intervention by the study hospitals. The monitoring of BARMER includes e.g. to perform random checks of whether a valid declaration of consent exists for insured patients whose health insurance data have been retrieved for treatment support. The steering committee, consisting of members of the TOP study group, will meet via telephone conferences twice a month to review the progress of the study and to make decisions within the framework of the study if necessary. The participating SHIPs, the study hospitals and the software provider will be responsible for providing data to the evaluation team. A designated advisory board will provide advice on the design, conduct and analysis of the trial. The data monitoring committee, consisting of members of the SHIPs, the hospitals accompanying the study, the software provider and the evaluation team, will be independent of the institution funding the study and of competing interests.

Results of the study will be disseminated through publications in international, peer-reviewed journals and conference contributions. The reporting of the results will adhere to the CONSORT Statement extension for cluster-randomised trials [55].

DISCUSSION AND LIMITATIONS

The present study investigates a complex CDSS-based intervention to optimise the process of inpatient medication therapy at admission, during the patients' stay in hospital, and at discharge, to prevent inappropriate medication use and thus promote patient safety. The method used is a hybrid type-1 effectiveness-implementation C-RCT with a stepped-wedge design, addressing besides effectiveness as the primary focus, the implementation of the TOP intervention as well. In the transition and intervention phase, patients will be offered an intensified pharmaceutical care at admission to hospital, during their inpatient stay, and on discharge. MTM is a key component of the intervention and will be carried out electronically using CDSS-based software. During the control phase (control group) patients will receive care according to respective hospitals standard.

Different data sources are linked to gain extensive insights into the effects of the intervention, in particular claims data from two statutory health insurance providers (SHIPs), self-reported patient data, and CDSS software data. The comprehensive process evaluation will contribute to a deeper understanding of how different components of the interventions will work and will provide insights into the implementation process, barriers to and factors facilitating implementation.

This study has limitations. As organisational and structural changes are being addressed, blinding is not possible. In addition, language barriers may also reduce the response rate, as the questionnaire will only be available in German. Due to convenience sampling at hospital level, it may in addition be that the hospitals participating in the study are already more receptive to MTM and aware of the technical possibilities for its realisation compared to other hospitals in Germany. Since some hospitals have already established programmes for MTM, they start with better preconditions than others, potentially influencing various study endpoints.

TRIAL STATUS AND REGISTRATION INFORMATION

Hospital recruitment began with the project's start in October 2020. Start of the C-RCT was August 2021, while the first participant enrolment was planned for 15/09/2021 and has started in November 2021. The last patient in will be at the end of January 2024 and the 3-month follow-up will be accordingly completed at the end of April 2024. Data collection will be completed by the end of August 2024. Analyses will be completed in September 2024.

Registration of the trial was initiated before the start of the C-RCT (August 2021), displayed on the public website after the start of the C-RCT (09/09/2021) but before the date of the first enrolment of participant (planned for 15/09/2021, with the first valid enrolment in November 2021).

ABBREVIATIONS

ATC code	Anatomical Therapeutic Chemical code
BUW	Bergische Universität Wuppertal
CDSS	Clinical decision support system
CEA	Cost-effectiveness analysis
CFIR	Consolidated Framework for Implementation Research
CONSORT	Consolidated Standards of Reporting Trials
C-RCT	Cluster-randomised controlled trial
CUA	Cost-utility-analysis
DDD	Defined daily dose
GEE	Generalised estimating equations
(G)LMM	(Generalised) linear mixed models
HCP	Healthcare professionals

ICC	Intra-class correlation coefficient
ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental cost-effectiveness ratio
IT	Information technology
MTM	Medication therapy management
PREMs	Patient-reported experience measures
PROMs	Patient-reported outcome measures
SEIA	Socio-economic impact assessment
SHIPs	Statutory health insurance providers
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SWD	Stepped-wedge design
TIDieR	Template for intervention description and replication
TOP	Transsektorale Optimierung der Patientensicherheit

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DISCLAIMER

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

AVAILABILITY OF DATA AND MATERIALS

Data collection forms and datasets generated and analysed during the current study are not publicly available, as participant consent and German regulatory instances restrict data use to the research team but they are available from the corresponding author on reasonable request and with permission of all involved institutions.

AUTHOR CONTRIBUTIONS

RB drafted the first version of the manuscript with input from JK-N and SM. Critical revision of manuscript for important intellectual content: SS, DL, AP, IM and JK-N. SM, DL, AP, DG, CK, IM, WG, JK-N, are responsible for study concept and design. AD is the study director. Acquisition of data: SM, SS, DL, AP, PI, IM, WG, JK-N and TOP study group. Analysis and interpretation of data will be performed by SM, SS, DL, AP, IM, WG, JK-N. PI is responsible for data management and the trust centre. JK-N is

the chief investigator of the study and is also the guarantor. All authors reviewed the paper and read and approved the final manuscript.

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COMPETING INTERESTS

SM, DL, PI, SS, CK, AD, KCR, IM, WG, JK-N 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 a family member of DG 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. All other authors have no competing interest to declare.

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FIGURE LEGENDS

Figure 1 Roll-out including follow-up of the C-RCT in a stepped-wedge design

Figure 2 Study sections

Figure 3 Socio-economic Impact Assessment (SEIA) - addressed levels

	C-RCT (33 months)					
	month 1-6	**month 7-12**	**month 13-18**	**month 19-24**	**month 25-30**	**month 31-33**
	tests at two accompanying hospitals					
cluster 1	*control phase*	*transition phase*	*intervention phase*			follow-up
cluster 2	*control phase*		*transition phase*	*intervention phase*		follow-up
cluster 3	*control phase*			*transition phase*	*intervention phase*	follow-up

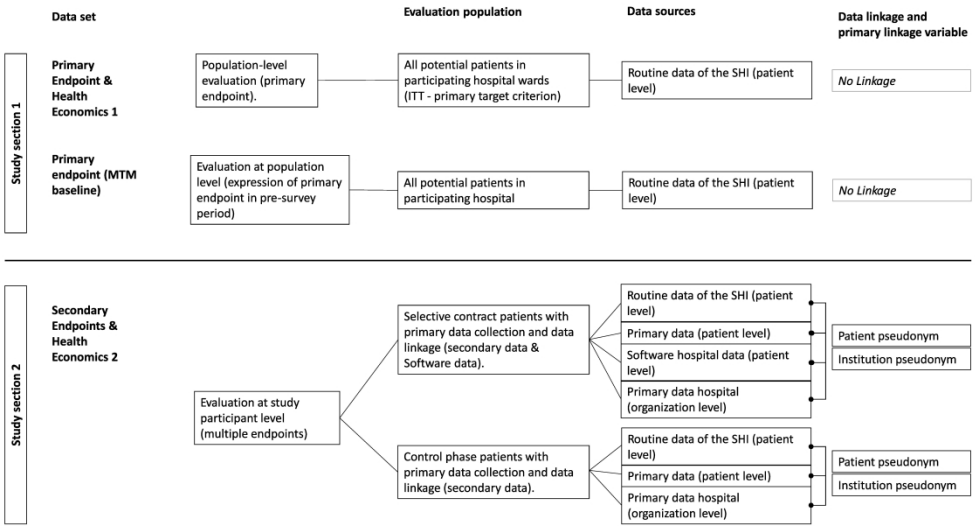

Figure 2 Study sections

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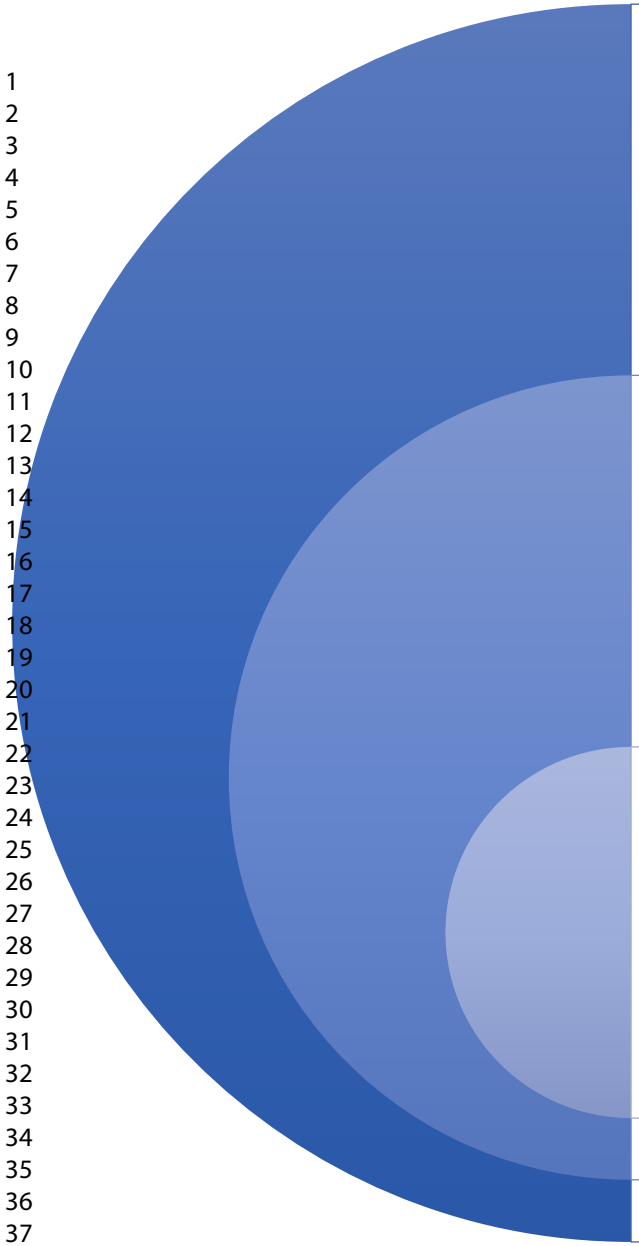

Policy level	• Upscaled, societal SER • *„Should this become the way of doing things?“*
Service level	• Service SER, ROI and time to break even • *„Under what conditions is the service viable?“*
Individual / organisational level	• Service-related costs and benefits • *„Under what conditions do we want to get involved?“*

SER = Socio-economic return, ROI = Return on investment

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Check
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	✓ *(p.1)*
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	✓ *(p.3)*
	2b	All items from the World Health Organization Trial Registration Data Set	✓
Protocol version	3	Date and version identifier	✓ *(p.21)*
Funding	4	Sources and types of financial, material, and other support	✓ *(p.20)*
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	✓ *(p.20)*
	5b	Name and contact information for the trial sponsor	✓ *(p.20)*
	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	n.a.
	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)	✓ *(p.18)*
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	✓ *(p.4-5)*
	6b	Explanation for choice of comparators	✓ *(p.4-5)*
Objectives	7	Specific objectives or hypotheses	✓ *(p.5-6)*
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)	✓ *(p.6-7)*
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	✓ *(p.7)*

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)	✓ *(p.7-8)*
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	✓ *(p.8-9 & online supplemental 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)	n.a.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n.a.
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n.a.
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	✓ *(p.10-11)*
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)	✓ *(p.7,10-11 & online supplemental file 2 & 4)*
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	✓ *(p.14)*
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	✓ *(p.7-8)*
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	✓ *(p.8)*
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	n.a.
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	✓ *(p.8)*
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n.a.
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n.a.
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	✓ *(p.11-13)*
	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	n.a.
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	✓ *(p.13-14)*
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	✓ *(p.14-15)*
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	✓ *(p.15-16)*
	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)	n.a.
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	✓ *(p.18)*
	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	n.a.
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	✓ *(p.12)*
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n.a.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	✓ *(p.17-18)*
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)	✓ *(p.17)*
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	✓ *(p.17)*
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
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	✓ *(p.13)*

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	✓ *(p.21)*
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	✓ *(p.20)*
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	n.a.
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	✓ *(p.18)*
	31b	Authorship eligibility guidelines and any intended use of professional writers	✓ *(p.20)*
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n.a.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	✓ *(online supplemental 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	n.a.

*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.

Table 1 Components of TOP intervention

Brief name	What?	Why?	How?	Who?	Where?	When and how much?
Electronically available treatment-relevant information at hospital admission	Anamnesis support on admission	Recognising inadequate outpatient pretherapy, avoiding errors in anamnesis	Making treatment-relevant information electronically available from health insurance data	Pharmacist (ward pharmacist or hospital pharmacist)	Access by computer using the TOP software in all parts of the participating hospital admitting patients (accident & emergency services, wards, pharmacy)	Once, when patient is admitted to hospital
MTM at hospital admission	Structured medication review on admission	Recognising prescription errors, correctly interpreting adverse drug reactions, reduction of prescription cascades, avoidance of treatment errors due to missing information	Electronically supported MTM review with subsequent recommendation for correcting inadequate medication therapy, medication reconciliation (between patient self-reports and health insurance data), documentation and communication of possible or necessary adjustments of medication	Pharmacist (ward pharmacist or hospital pharmacist), physician in patient`s department	Access by computer using the TOP software in all parts of the participating hospital admitting patients (accident & emergency services, wards, pharmacy) Communication of adjustments to medication therapy through hospital information systems, by email or phone	Once, when patient is admitted to hospital

MTM during hospital stay	Co-care of high-risk patients during their hospital stay	Improving MTM in the hospital, reducing mortality and complications in the hospital, avoidance of treatment errors	Electronically supported MTM review for inpatient medication therapy of high-risk patients	Pharmacist (ward pharmacist or hospital pharmacist)	By computer using the TCP software	Daily during patient`s hospital stay
MTM at discharge from hospital	Medication checking and recommen-dation of medication therapy at discharge	Reducing medication errors	Electronically supported MTM review with subsequent recommendation for correcting inadequate medication therapy, documentation and communication of possible or necessary adjustments to medication, comparison of the final therapy recommendation to previous medication	Pharmacist (ward pharmacist or hospital pharmacist), physician in patient`s department	By computer using the TCP software Communication of adjustments to medication therapy through hospital information systems, by email or phone	Once before patient is discharged

Medication information of patients at discharge from hospital	Patient empowerment at discharge	Informing the patient about medication after discharge to improve health literacy, autonomy and adherence, reducing application errors	Pharmaceutical discharge interview (face-to-face) including information about BMP (printed handout of medication therapy), information regarding supplemental self-medication, therapy supporting notes via app	Pharmacist (ward pharmacist or hospital pharmacist)	The interview takes place in the patient`s room or in a room of the department or pharmacy	Once before patient is discharged
MTM-coordination at discharge from hospital	Cross-sectoral coordination at discharge	Reducing medication errors and avoiding information breaches between sectors, avoidance of treatment errors due to insufficient cross-sectoral coordination	Coordination of changes to therapy with the general practitioner who continues treatment	Pharmacist (ward pharmacist or hospital pharmacist), general practitioner	Communication of adjustments to medication therapy through information systems, by email or phone	If necessary, once before patient is discharged

MTM: medication therapy management

Table 2 Implementation strategies of TOP

Name it: ERIC Implementation strategy	Operationalise it								
	Action	Actor	Context	Dose	Action Target		Temporality	Implementation Outcome	Justification
					Conceptual	Unit of Analysis			
Use evaluative and iterative strategies									
Assess for readiness and identify barriers and facilitators	Assessing facilitators for and barriers to implementing the TOP intervention through collected field notes and assessment of determinants of implementation (e.g. resources and attitudes of healthcare professionals - HCPs) through written questionnaires	HCPs (physicians and pharmacists) in the hospitals for data collection through questionnaires, TOP study team for collecting field notes and analysis of the data collected	Assessment and analysis electronically, written questionnaire is sent to the HCP to fill in during the hospital shift	Field notes are collected continuously, data collection with HCP through written questionnaire twice during the study	Context	Hospital-based	Field notes: transition and intervention phases; written questionnaire: control and intervention phases	Barrieres to and facilitators for implementing the TOP intervention	To analyse and control the organisation-related factors which may have an influence on the degree of TOP implementation and the outcomes measured in study setting.

Stage implementation scale-up	For implementing the TOP intervention, there are two hospitals accompanying the study, which will implement the intervention before the C-RCT starts.	Two hospitals accompanying the C-RCT	Pharmacists (and physicians) at the accompanying hospitals implement and test the TOP intervention in routine care	Implementation takes place once in each accompanying hospital	Assistance to implementation	Hospital-based	In the preparation phase of the study (10 months before C-RCT starts)	Barrieres to and facilitators for implementing the TOP intervention, necessary adaptations of TOP intervention and its implementation process	TOP is a complex intervention that is to be introduced into routine care for the first time in 12 hospitals. To optimse the implementation process and intervention itself before it is tested in the study.
Provide interactive assistance									
Centralise technical assistance	The two accompanying hospitals provide technical assistance on all issues of implementing the TOP intervention into routine care for hospitals included in the study if questions arise and support is needed.	Pharmacists at the accompanying hospitals in coorperation with the software developer/support team, pharmacists of study hospitals	Support is offered by phone, email and through online meetings	Support is offered as needed, online meetings once a week	Context, implementation and mechanism of impact	Hospital-based	Transition and intervention phase	Barriers and facilitators, adaptations, fidelity, feasibility, response	To support the study hospitals in the best possible implementation of the TOP intervention.

Adapt and tailor to context									
Promote adapta-bility	Tailoring the intervention to the given structures and processes of every study hospital (organisation-specific implementation-plans).	Pharmacists (and physicians) of the accompanying and study hospitals, TOP study team	Remotely by email, phone or in online meetings	Tailoring is offered as needed	Imple-menta-tion and effec-tiveness	Hospital -based	Transition and intervention phase	Adaptations to intervention, fidelity, acceptability	To implement the TOP intervention into routine care, it is necessary to observe and take into account the given stuctures and processes of every health facility because they may differ as a function of the size of the hospital, patients, processes etc..

Develop stakeholder interrelationships									
Organise clinician implementation team meetings	Build structures for an information exchange between the pharmacists (and physicians) at the study hospitals	Pharmacists (and physicians) and key persons at the accompanying and study hospitals, TOP study team	In online meetings, in person	Online meetings with pharmacists once a week, online meetings with study hospitals once a month, and if necessary, in-person meetings (once a year)	Implementation and mechanism of impact	Hospital-based	Transition and intervention phase	Acceptability, appropriateness, feasibility	Use of lessons learned can improve the implementation process and acceptability, appropriateness and feasibility of the intervention.
Train and educate stakeholders									
Conduct educational meetings	Educational meetings are held for key persons and HCPs on different topics (e.g. intervention details like process training, rules for reviewing indications for medication therapy, study details like evaluation of the TOP intervention)	TOP study team, key persons and HCPs at the two accompanying and study hospitals, software developer team	In online meetings, in person	Online meetings with pharmacists once a week, online meetings with study hospitals once a month and as necessary	Implementation	Hospital-based	Established early in the control phase of the C-RCT, maintained throughout the C-RCT	Fidelity, acceptability	Educational training is a necessary but insufficient strategy for behavioural change. Building knowledge is important for laying the foundation for the actual application of the intervention components.

Engage consumers									
Use mass media	Information on the TOP intervention is placed in newspapers, information materials (in print and online) by particpating statutory health insurance providers (SHIPs)	SHIPs, TOP study team	In print and online	Established early in preparation phase of the C-RCT, maintained over time	Recruit-ment and imple-menta-tion	Patient-based and hospital -based	Preparation and C-RCT phase	Recruitment and reach of intervention (patient-level)	Receiving information about the TOP intervention could improve patients` commitment to being involved in the study and thus improve the patient-related reach of the intervention.

Utilise financial strategies									
Use capitated payments	TOP intervention is part of a funded project of the G-BA, the hospitals receive financial support (e.g. amount per patient for an intervention delivered to the patient, hospitals receive funds for implementing the TOP software and hiring staff)	SHIPs, Funder: G-BA	Funds are transferred electroni-cally	Payments for financial support per patient are delivered depending on the number of patients recruited for the study, one-off payments for infrastructural support	Imple-menta-tion and mecha-nism of impact	Patient-based and hospital-based	Amount per patient: transition and intervention phase, infrastructural payment: transition phase	Reach of intervention (patient and hospital level), feasibility	Implemen-ting a new form of care is a highly complex process of change in the routine care of the hospitals, which are subject to financial pressure anyway. Financial support is necessary to optimise the implementa-tion and use of new interventions like TOP.

Table 3 Data collection of process evaluation

Focus	Assessment	Measurement point
Domain – Context: In which context and setting does the intervention take place? What are the determinants of implementation?		
Hospital level		
Hospital baseline data on organisational-structural conditions, e.g.: - Organisational structures and processes - Organisational culture - Organisational Readiness for Implementing Change	Written survey: key person at the hospital (e.g. management, project manager)	Control phase
Staff baseline data on organisational-personnel readiness, e.g.: - Professional background - Interprofessional collaboration - Organisational Readiness for Implementing Change - Acceptance and Use of Technology	Written survey: pharmaceutical and medical staff	Control phase
Patient level		
Patient baseline data, e.g.: - Socio-demographic data - Previous experience with MTM and components of the TOP intervention	Written survey: enrolled patients	Shortly after discharge from hospital (t0)
Domain – Context: What factors inhibit or promote implementation of the intervention? How is the intervention implemented in health care practice?		
Hospital level & Patient level		
Inhibiting and promoting factors	Document analysis	Transition and intervention phases
Hospital level		
Implementation status, e.g.: - Status of technical implementation - Status of implementation of TOP processes	Document analysis	Transition and intervention phases

Domain – Recruitment: Who receives the intervention?		
Hospital level		
Data on representativeness, e.g.: - Structural variables of alternative hospitals	Data extraction with survey form	Control phase
Participation information, e.g.: - Reason for participation - Implementation policy and practices, resources - Tension for change, public needs (CFIR)	Interview: key person at the hospital (e.g. management, project manager)	Transition phase
Patient level		
Data on the recruitment process, e.g.: - Number of consents	Document analysis	Control, transition and intervention phases
Domain – Implementation: Is the intervention implemented and applied in principle, as planned? To what extent is the intervention implemented and applied?		
Hospital level		
Implementation process and implementation outcomes, e.g.: - Appropriateness, feasibility, acceptability	Written survey: pharmaceutical and medical staff	Intervention phase
- Implementation of intervention according to standard, adaptations to the interventions - Fidelity, dose, reach	Document analysis	Transition and intervention phases
Patient level		
Implementation process and implementation outcomes, e.g.: - Perception and evaluation of intervention components such as contact with pharmacist - Reach, dose	Written survey: enrolled patients	Shortly after discharge (t0) and approximately 90 days after discharge (t1)
	Document analysis (software data)	Intervention phase

Domain – Mechanisms of impact: How is the intervention accepted by those involved? What are the unintended consequences and how are they to be evaluated?		
Hospital level **Response, e.g.:** - Intervention evaluation and attitudes towards TOP intervention - Interprofessional collaboration - Use of intervention in work routine (normalisation process)	Interview and written survey: pharmaceutical and medical staff Document analysis (software data)	Intervention phase Intervention phase
Patient level **Response, e.g.:** - Attitudes to and experiences of TOP intervention	Interview: subsample of enrolled patients	After discharge from hospital, Intervention phase
Domain – Effectiveness: How effective is the intervention, as perceived by the participants? How are the results to be interpreted in relation to the targeted outcome parameters (primary and secondary outcomes)?		
Hospital level **Sustainability, e.g.:** - Organisation-related expectations of the intervention met - Intentions for continuation **Reflection of the implementation process**	Interview: key person at the hospital (e.g. management, project manager) Interview: inter-hospital group of experts	Intervention phase/follow-up phase Intervention phase/follow-up phase

Transsektorale Optimierung der Patienten-sicherheit

Information for patients on participation in the project "Trans-sectoral optimisation of patient safety" (TOP)

Dear Patient,
We would like to provide you with this information for patients about the TOP project, which aims to improve the safety of medication therapy during a hospital stay and avoid adverse drug reactions, and encourage you to participate in the project.

What is the aim of the project?
When you are admitted to hospital there is often insufficient information available about your current medication and your medical history. In addition, hospital pharmacists rarely support the treating physicians in the treatment of patients in hospitals.
In the TOP project everyone works closely together to identify medication errors and avoid adverse drug reactions. With the help of specially developed software, hospital pharmacists check your medication and regularly exchange information for optimal medication therapy with your hospital doctors. In particular, patients who suffer from several illnesses and are taking several medications at the same time will benefit from this project. In this way, patients who have a particularly high risk of drug interactions due to their previous history or their current medication are also identified in time. They are monitored particularly closely by the hospital pharmacists.
Another new feature is that hospitals can now obtain information about your medical history from your statutory health insurance to help them plan and provide optimum care for your medication. For this purpose, participating hospitals are connected to the computer data centre commissioned by your statutory health insurance via a technical network. Using the software, hospitals receive information at short notice about which medicines, therapeutic aids and appliances have been prescribed to you in the last 3 years and which diagnoses and treatments are documented, as well as information about co-treating physicians and therapists. Additionally, the exchange with your general practitioner is ensured by structured discharge management in this project.

You can find further information in the "Information for patients on the processing of personal data".

Scientific evaluation
The TOP project is scientifically monitored and evaluated by the University of Wuppertal in cooperation with the University of Bielefeld and the University of Cologne. As part of the evaluation, the scientists check whether the new measures can prevent damage to health.
Scientific evaluation is carried out on the basis of data on your medical history and prescribed medications provided by your statutory health insurance and the data documented in the software. Surveys and interviews are another elementary component of the evaluation, because your personal experiences are of particular importance to us. Those data will be collected after your hospital stay. If you have agreed to be contacted by post, the questionnaires will be sent to you by your statutory health insurance. Further information on data collection for the evaluation is attached to this questionnaire.

How can I participate in the project?

After receiving detailed information about the project and the procedure, you state your willingness to participate in the project by signing the statement of participation and declaration of consent. This statement is also valid for further stays in the same hospital until the end of the project.
Participation begins on the day of signing. With your signature, you authorize the hospital to collect data on your medical history held by your statutory health insurance to check your medication therapy. Participation in the TOP project is voluntary and free of charge. There will be no disadvantages for you if you decide not to participate.

Can I end my participation in the TOP project?
Your participation ends automatically when your insurance relationship with your statutory health insurance ends or when the project ends. Your agreement to participate can be withdrawn at any time; you do not need to give any reasons for doing so, and this will not have any negative effects on your medical treatment. You only need to state in wirting that you wish to cancel your participation and send the cancellation letter to your statutory health insurance.
However, your withdrawal only takes effects from the time you declare it. It has no retroactive effect. The processing of your data up to that point in time remains lawful.

Information for patients on the processing of personal data (TOP) (abbreviated version)

First things first: BARMER, AOK Nordost, their contractual partners and the service providers involved are very conscientious about data protection.

Your personal data is processed on the basis of sections 63, 284 and 295a of Book V of the Social Code as well as the statement of consent to data processing given by you. As part of your participation in the TOP project, a variety of data and information collected from you and about your treatment is stored and processed:

Participation data
Your signed statement of participation and consent will be archived by the hospital in your medical records. In addition, your participation will be documented by your statutory health insurance in your electronic patient file.

Data on medical documentation
The hospitals participating in the project collect medical data from you as part of your inpatient treatment. This data is part of standard medical documentation. The documentation on your current treatment is stored on the hospital server. Your statutory health insurance has no access to the patient data generated at the hospital.

Data in connection with past treatments and prescriptions
As part of your participation in the TOP project, your statutory health insurance will provide the hospital with all the information about your medical history in the past 3 years that is necessary and important for your treatment. It will provide this information digitally using special software. By signing the statement of participation and declaration of consent, you agree that participating hospitals may view the data on your medical history held by your statutory health insurance as soon as you have signed the statement.

Use of software
The TOP project uses special software which transmits the health insurance data to the hospitals in encrypted form. This software also documents your current treatment data and medications. Only authorised hospital employees have access to the software and to your data. The hospital will access the software over a specially secured data connection from the hospital to the data centre of your statutory health insurance. At the end of the project or when a hospital leaves the project, the hospital`s access rights to your data will be blocked by your statutory health insurance.

Information for general practitioners on current prescriptions
In your general discharge documents, your referring doctors receive therapy recommendations for your further treatment. In addition to the current national medication plan, they will also receive information on whether and why the medication has been changed.

Scientific monitoring and evaluation without disclosure of your name
The University of Wuppertal in cooperation with the University of Bielefeld and University of Cologne will evaluate the medical data related to your personal treatment. This concerns data collected during your hospital stay, information documented in the software, and data from your statutory health insurance. In addition, data is collected via surveys and interviews. All this data will be linked together during scientific evaluation. The universities commissioned with this evaluation will only be provided with your personal data once it has been pseudonymised. This means that your name and other identifiers (e.g. insurance number) are replaced by labels. Therefore, it will not be possible to make inferences about your identity.

Data protection and data processing
Your personal data will be used only to carry out the contractual tasks of the project. The collection, processing and use of data are governed by applicable provisions on the protection of social data according to the German Social Code and on the protection of personal data in accordance with the General Data Protection Regulation (GDPR)) and, if applicable, the Federal Data Protection Act as amended from time to time. Your statutory health insurance and its project partners are obliged to comply with all data protection regulations. This also applies after your treatment ends.

Data storage at your statutory health insurance & at the hospital
Your participation data collected during the project and stored by your statutory health insurance will be deleted in accordance with statutory provisions when you leave this project, to the extent that they are no longer required for complying with statutory provisions, and otherwise no later than10 years after the end of your participation. At the end of the project or when a hospital leaves the project, the access rights of participating hospitals to patient-related data on their medical history will be blocked at your statutory health insurance.

Consent and revocation of consent to data processing
The data processing described is only permitted if you have consented to such processing. Your statement of consent forms part of your statement of participation. Without your consent, participation in the project is not possible. You can withdraw your statement of participation and declaration of consent at any time by writing your statutory health insurance; you do not need to give reasons. Further information can be found in "Information for patients on participation".

Transsektorale Optimierung der Patienten-sicherheit

Statutory health insurance		
Name of the insured person		Date of birth
Cost unit identifier	Insured person number	Status
Registration number of healthcare institutions	Physician identifier	Date

QR-Code

DECLARATION OF CONSENT AND STATEMENT OF PARTICIPATION IN THE PROJECT: "TRANS-SECTORAL OPTIMISATION OF PATIENT SAFETY"

1. Statement of participation:

I hereby declare that
- I would like to participate in the TOP project.
- I have received detailed and understandable information about the contents and objectives of the project and the processing of my data that will be required to carry out the project. I have had sufficient opportunity to discuss the implementation of the project. All my questions were answered satisfactorily.
- I have received, read and understood the "Information for patients on participation" and the "Information for patients on data processing".
- I am aware that my participation in the project is voluntary.
- I am also aware that my participation in the project begins with the signing of this participation and consent form. My participation will end if I withdraw this statement, when the project ends or I am no longer insured with BARMER.

Cancellation policy
I can withdraw my statement of participation in writing, without giving reasons, at any time. I will not suffer any disadvantages.
By post:
E-mail:

. . _____

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

2. Declaration of consent

I have received the “Information for patients on participation” and the “Information for patients on data processing” and have taken note of them. I consent to the collection, processing and storage of my personal data as described and required for the project.

I agree that:

- The hospital will transmit my participation data (name, date of birth, insurance number and start of participation) electronically to my statutory health insurance provider.
- During my hospital stay, the hospital may retrieve data on my treatments and prescriptions in the past 3 years from my statutory health insurance. Details are described in the "Information for patients" provided to me. I am aware that the data will be retrieved at any time after my signature. On the basis of this data hospital pharmacists will carry out a detailed review of my medication therapy.
- Upon discharge, the hospital will provide the referring doctors with a therapy recommendation for further medication and, if necessary, contact them for a personal discussion.
- My signed statement of participation and declaration of consent will be stored in my patient file at the hospital and my statement of participation is documented in the software. My statutory health insurance will store my participation data (start of participation, hospital) in the electronic insurance file (eFile).
- My data will be treated confidentially by the hospital and by my statutory health insurance in compliance with applicable data protection regulations.
- My health insurance data will be processed for the purposes of scientific analysis (evaluation) by the scientific institutes involved in the project. My medication data may be retrieved from the database held by my statutory health insurance for checking against the criteria for participation in the project and for the scientific evaluation. Pseudonymised means that my name and other identifiers (e.g. insurance number) will be replaced by labels that rule out me being identified.
- My statutory health insurance provider may send me survey questionnaires by post to evaluate the project.

I acknowledge that

- In the context of this project, personal data will be processed in a way that goes beyond the usual scope of medical treatment - but which is important for the success of the project.
- My data will be processed by the hospital, my statutory health insurance and the evaluation team in compliance with applicable data protection regulations.

Cancellation policy
I can withdraw my statement of participation in writing without giving reasons, at any time. I will not suffer any disadvantages.
By post:
E-mail:

. . _____

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

Information for patients on the scientific monitoring and evaluation of the project *„Trans-sectoral optimisation of patient safety“* (TOP)

Dear Sir or Madam,
We would like to ask you whether you would like to take part in the data collection (surveys, telephone interviews, document analysis, analysis of claims data) being carried out by the University of Wuppertal together with the University of Bielefeld and the University of Cologne. The data collection is part of the scientific monitoring of the project "Trans-sectoral Optimisation of Patient Safety - TOP", which was initiated by BARMER.

Please read the evaluation information carefully and ask questions if you do not understand something.

Medication therapy is an essential component of the medical treatment of patients. In hospitals, several parties are involved in the process of medication treatment from admission to discharge. Inadequate information transfer or coordination between hospital staff and general practitioners (GPs) can have various consequences for patients. For example, there is a risk of drug interactions occurring or the patient may be hospitalised again.By implementing a new form of care, the aim is to achieve intensified and therefore improved pharmaceutical care for patients. The medication process in hospital will be supported electronically from admission to inpatient treatment through to discharge. The aim is to avoid interactions and unnecessary hospitalisation and to improve quality of life.

With your support, we would like to analyse the effects of this new form of care. This will examinewhether an improvement in the medication management of hospitalized patients can be achieved.

What is the evaluation process and what data do we need?
The evaluation will run from August 2021 to May 2024, during which time the new form of care will be introduced in your hospital (by mid-2023 at the latest) alongside the normal form of care. The implementation of the new form of care will result in changes to hospital processes. It may therefore not be visible to you whether the new form of care has already been introduced in your hospital. Whether and to what extent the new form of care is implemented at the time of your stay in the hospital treating you will be decided at random.

If you have decided to participate in the project and the evaluation, you will receive **two questionnaires over a period of three months**. The questionnaires will be sent to you by post by your statutory health insurance provider (SHIP). Depending on when and in which department you were hospitalised, an employee of the University of Wuppertal will also contact **you by telephone** once after **your hospital discharge**.. In addition to the questionnaires and the telephone interview, project staff will gain **insight into your discharge documents.**

What happens to your data (data protection information)?
All information and statements that you provide in the written questionnaires and the information from the discharge documents are collected in pseudonymised form. Pseudonymisation means that your name and other identifiers (e.g. insurance number) are replaced by labels. Therefore, it will not be possible to make inferences about your identity.An identification list, which makes direct personal reference possible, is managed by project staff of SHIPs and kept under lock and key. These persons are bound to secrecy. In a further step, the pseudonymised data from the written surveys is linked to your pseudonymised claims data of SHIPs. The purpose of the link is to combine the data of the same person for scientific analysis. The data is linked using an encryption procedure and is carried out by an independent trust centre. The project team of the universities involved in the evaluation will be granted access to the linked data set for scientific analysis. In addition, your contact details (name, telephone number) may have been collected by the hospital project team during your hospital stay. After your consent to the scientific monitoring and evaluation, this information will be forwarded to the project team at the University of Wuppertal, who may contact you to arrange an appointment for the telephone interview.The telephone interview is recorded using a tape recorder and then transcribed. All information is anonymised, i.e. names, places and other personal details are changed so that it is no longer possible to draw conclusions about individual persons. The personal data (name, telephone number) will be stored separately from your survey and health data at the University of Wuppertal and will be completely deleted after the end of the research project. This ensures that the data is anonymised after the end of the project.

We assure you that all persons involved will comply with the data protection laws. The legal basis for the processing of the data is in accordance with the General Data Protection Regulation (GDPR).

Who can I contact if I have any questions?
The University of Wuppertal will be happy to answer your questions at any time.

Consent and revocation of consent
Participation in the evaluation is voluntary. If you agree to participate, please confirm your consent by signing the enclosed form (Declaration of consent for scientific monitoring and evaluation). You can revoke your declaration of consent at any time in writing without giving reasons and without any disadvantage to you. If you withdraw your consent, no further data will be collected. The data already collected and processed up to the time of your revocation will be anonymised and can therefore no longer be attributed to you personally. Your personal data (e.g. name, telephone number) will be deleted together with your entry in the identification list.

Declaration of consent for patients for scientific monitoring and evaluation of the project *Trans-sectoral optimisation of patient safety* - TOP

I have been sufficiently informed about the contents of the evaluation and its procedure. I have read the enclosed "Information for patients on scientific monitoring and evaluation". I have had the opportunity to ask questions and have received satisfactory and complete answers. I have had sufficient time to decide to participate in the evaluation and realise that participation is voluntary. I am aware that my data will be processed pseudonymised. The withdrawal of consent does not affect the lawfulness of processing based on consent before its withdrawal. In the event of revocation, no further data will be collected. In this case, I can arrange for the data to be deleted.

I am aware that personal data about me, as described in the attached "Information for patients on scientific monitoring and evaluation", will be collected and recorded at the University of Wuppertal.

I agree that the data will be stored for at least 10 years after completion or discontinuation of the study and subsequently only archived in anonymised form (without personal reference).

Changes to the evaluation data (e.g. correction or deletion of individual details) are possible until the time of anonymisation (after the evaluation has ended). I know that I can withdraw my consent to participate in the evaluation at any time and without giving reasons, without any disadvantages for my further medical care. If I withdraw my participation, I can request the deletion of all data collected to date that has not been anonymised. To have the data deleted, please get in touch with the contact person at the University of Wuppertal..

I have been informed about my data protection rights. I agree to the collection, processing, storage and transmission of the data in pseudonymised form. I also agree that my pseudonymised data from the written survey may be linked to my pseudonymised claims data of SHIP and I also agree that if an employee of the hospital has recorded my contact details (name and telephone number) during my inpatient stay in order to organise the telephone interview, these will be forwarded to the University of Wuppertal.

I will not incur any costs or other obligations by participating in the evaluation. I have received a copy of the information sheet and this declaration of consent.

I hereby declare my voluntary participation in this evaluation. At the same time, I give my consent for the project team to conduct the surveys and interviews and to inspect my discharge documents. I also agree that my data from the written survey may be linked with my pseudonymised claims data of SHIP and, if applicable, with the medication data of the hospital for the scientific evaluation using an encryption procedure.

Participant:

Surname, first name *(block capitals)*	***Place and date*** *(to be filled in personally)*	***Signature***