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Integrating the clinical pharmacist into the emergency department interdisciplinary team: a study protocol for a multicentre trial applying a non-randomised stepped-wedge study design

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ABSTRACT

Introduction The 'emergency department (ED) pharmacist' is an integrated part of the ED interdisciplinary team in many countries, which have shown to improve medication safety and reduce costs related to hospitalisations. In Norway, few EDs are equipped with ED pharmacists, and research describing effects on patients has not been conducted. The aim of this study is to investigate the impact of introducing clinical pharmacists to the interdisciplinary ED team. In this multicentre study, the intervention will be pragmatically implemented in the regular operation of three EDs in Northern Norway; Tromsø, Bodø and Harstad. Clinical pharmacists will work as an integrated part of the ED team, providing pharmaceutical care services such as medication reconciliation, review and/or counselling. The primary endpoint is 'time in hospital during 30 days after admission to the ED', combining (1) time in ED, (2) time in hospital (if hospitalised) and (3) time in ED and/or hospital if re-hospitalised during 30 days after admission. Secondary endpoints include time to rehospitalisation, length of stay in ED and hospital and rehospitalisation and mortality rates.

Methods and analysis We will apply a non-randomised stepped-wedge study design, where we in a staggered way implement the ED pharmacists in all three EDs after a 3, 6 and 9 months control period, respectively. We will include all patients going through the three EDs during the 12-month study period. Patient data will be collected retrospectively from national data registries, the hospital system and from patient records.

Ethics and dissemination The Regional Committee for Medical and Health Research Ethics and Local Patient Protection Officers in all hospitals have approved the study. Patients will be informed about the ongoing study on a general basis with ads on posters and flyers.

Trial registration number NCT04722588.

Strengths and limitations of this study

- The stepped-wedge design, recommended for complex interventions in healthcare (+).
- No spillover effect between study groups (+).
- Inclusion of the total emergency department populations in all included hospitals (+).
- No specialised training of the interdisciplinary teams (–).
- Inclusion from only three hospitals in Norway (–)·

INTRODUCTION

The main role of clinical pharmacists is to improve medication management to achieve the best possible health outcome for patients. More specifically, clinical pharmacists work to optimise medication therapy, identify and prevent drug-related problems (DRPs), and consequently minimise the risk of medication errors. This is traditionally done by medication history taking, medication reconciliation (MedRec), medication review (MedRev) and medication counselling, but requires working directly with patients, physicians and other healthcare professionals and includes communication to ensure that medications are correctly used.[1–6]

The employment of clinical pharmacists in hospitals has shown improvement in many aspects of medicines safety, for example, prescribing appropriateness with reduction of potentially inappropriate medications from 17.0% to 12.2%, reduction of potentially prescribing omissions from 2.2% to 0.7%[7] and increased appropriate use of antimicrobials with almost 80% acceptance rate of pharmacist recommendations.[8] Seven of twelve trials in a review by Kaboli *et al* reported on reduction of DRPs and medication errors.[9] In fact, studies indicate that more than 80% of DRPs can be identified and solved with clinical pharmacist

interventions.[10 11] Studies also show reduction in hard and costly endpoints such as hospital utilisations,for example, in the study by Liu *et al* where hospitalisation rate was reduced from 32.5% to 22.2% when a clinical pharmacist was included in the interdisciplinary team.[12]

The inclusion of clinical pharmacists in emergency departments (EDs) has become standard in many countries and has led to a reduction in identified medication errors by 78%,[13 14] reduced medication omissions and delay,[15] 12-hour shorter hospital stays per patient,[16] reduction in rehospitalisation by 5%,[17] and decreased mortality rates.[18] There is a wide range of services provided by clinical pharmacists in the ED that has shown an effect in various countries and settings.[19–21]

In Norway, implementation of the clinical pharmacists in direct patient care has progressed slowly compared with countries such as the USA and the UK, and the majority of all hospital departments do not yet have access to clinical pharmacy services.[22 23] For the few clinical pharmacists working in Norwegian EDs, no standardised workflow or procedure has yet been established. In this study, we will investigate the impact of implementing ED pharmacists as part of the interdisciplinary team in three EDs in Northern Norway. The aim of this study is to explore the impact on length of stay (LOS), rehospitalisation and mortality.

Hypothesis and objectives

Our hypothesis is that the intervention will affect time in hospital during 30 days after admission to the ED, combining time in ED during stay, time in hospital during stay if hospitalised and time in ED and/or hospital if rehospitalised within 30 days after each ED admission. This, in turn, will reduce time before the first unplanned rehospitalisation, number of hospital re-admissions and mortality, which again may reduce healthcare costs.

METHODS AND ANALYSIS

This protocol is developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement (see online supplemental file 1 for SPIRIT 2013 checklist).[24]

Study design

The implementation of clinical pharmacists into the ED interdisciplinary team is a complex intervention where interactions between the pharmacists and the rest of the team will change how the overall service is provided in addition to the tasks that the pharmacists will introduce into the ED. The number and variability of outcomes also point at the complexity of the intervention. Therefore, there has been permitted a degree of flexibility and tailoring. The effect of the intervention will be assessed applying a non-randomised stepped-wedge trial design.[25] A stepped-wedge design allows for the intervention to be rolled out sequentially, thus allowing to control for differences between study sites (vertical control) and long-lasting impacts (horizontal control) during the study period. This is the gold standard when a conventional randomised controlled trial is not possible.[25 26]

The intervention will be implemented in all three EDs over a 12-month period, starting with a 3-month control period in all EDs (planned start-up 1 February 2021). This period allows for baseline data collection before the intervention. After this period, we will consecutively roll out the intervention in 3-month intervals. Starting with the largest ED (Tromsø, 3 May 2021), continuing with the second largest (Bodø, 2 August 2021) and finally the smallest ED (Harstad, 1 November 2021), see figure 1, all EDs will have the intervention implemented during the last 3 months until the trial is terminated (planned 31 January 2022).

Study settings

This is a multicentre study including three EDs in Northern Norway Health Authority region; the University Hospital of North Norway (UNN) Tromsø, Nordland Hospital (NLSH) in Bodø and UNN Harstad with approximately 15 000, 12 000 and 6000 patients presenting annually in the respective EDs. The three EDs operate similarly and receive patients who need immediate healthcare in case of acute illness or injury. Norway has a well-functioning primary care system, including municipal urgent care clinics providing ambulatory care outside of general practitioner (GP) office hours. In order to be admitted to the ED, the patients need a referral either from GP or from a physician at an urgent care clinic. At the ED, the patient is met by an ED nurse and an ED physician (either an intern or a resident in specialty training), who perform the initial examinations and assessments of the patient. A senior physician is always on call in case of the need for a consultation. NLSH is the only ED with senior physicians situated in the ED during daytime. From the ED, patients are either admitted to a hospital ward, transferred to a municipally run health institution or discharged to their homes. Few EDs in Norway have pharmacists included in the interdisciplinary team, and many hospital wards do not have clinical pharmacist available.

Study population

All patients presenting to the EDs during the study period will be included in the study. Patients presenting during the

Month	1	2	3	4	5	6	7	8	9	10	11	12
Tromsø	C	C	C	I	I	I	I	I	I	I	I	I
Bodø	C	C	C	C	C	C	I	I	I	I	I	I
Harstad	C	C	C	C	C	C	C	C	C	I	I	I

Figure 1 The stepped-wedge study design showing the distribution of control (C) and the intervention (I) periods during a 12-month study period.

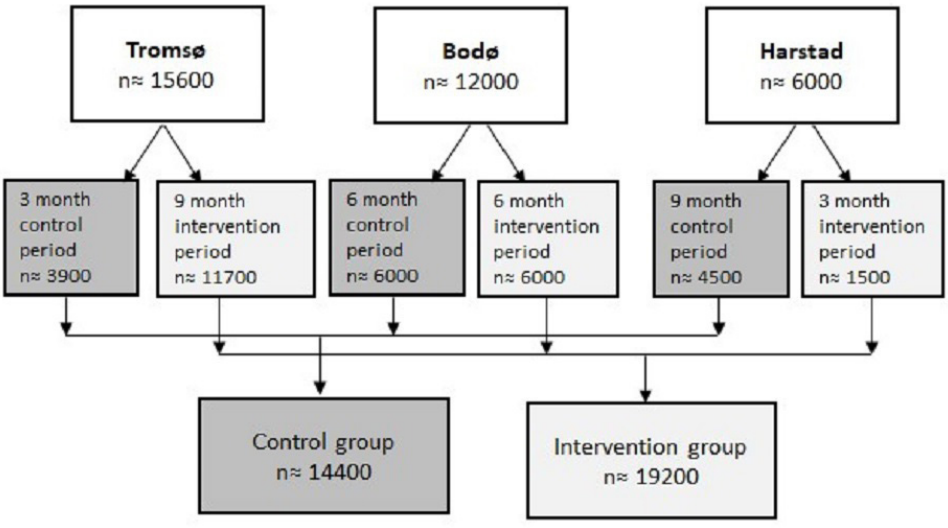

Figure 2 Flow chart of the anticipated population presenting to the emergency departments during the study period.

control period will be allocated to the control group (n≈14 400), while patients presenting during the intervention period will be allocated to the intervention group (n≈19 200), independently of whether they receive clinical pharmacist services or not, see figure 2. Patients, for whom data are not available retrospectively, will be excluded.

Randomisation and blinding

Neither EDs nor patients will be randomised. Randomising EDs would be preferable with the stepped-wedge design if a large number of EDs or equally sized EDs were included.

Neither staff nor patients will be blinded for the intervention, because it will be impossible to conceal the new member of staff. However, the ED pharmacists will be implemented as part of the daily-life work setting without announcing specifically to the patients that this is a new intervention.

Standard care delivered during control periods

The standard care procedures, which are similar in all three EDs, will be used in the control periods: Patients cared for in the EDs receive treatment from ED physicians and nurses, and no pharmacists are involved in any of the EDs. MedRec is usually performed by an intern or a resident in specialty training. The reconciled medication list is included in an admission note. The admission note is then uploaded to the electronic patient journal system that collects all patient medical data obtained in hospital. A standardised MedRev, by pharmacist standards, is not undertaken in the EDs. However, physicians may pause, change or add medications as appropriate. If the patient is admitted to hospital, the medications will be reviewed by physicians at the ward the proceeding day, where clinical pharmacists may be a part of the team.

On discharge, the patient's primary care physician (GP or institutional physician) receives a discharge summary. The discharge summary should include reasons for the hospitalisation, procedures and assessments made during admission and hospitalisation, and an updated medication list including a description of adjustments of medication therapy made during the hospital stay and recommendations for further follow-up. The primary care physician is responsible for follow-up of the patient and the patient's medication list after the hospital stay.

The intervention delivered during intervention period

During the intervention period, clinical pharmacists will be present in the EDs from 08:00 to 19:00 Monday to Friday. There will be two shifts, one shift is from 08:00 to 15:30 and another one is from 11.30 to 19.00. Consequently, there will be clinical pharmacists available in the EDs during the hours of the day when the majority of patients arrive, and the pharmacist's capacity is doubled during the busiest time of the day. Early mornings are normally relatively slow paced and the pharmacists may use this time to follow-up on patients admitted during the night (from 19:00 to 08:00), in particularly those who have been admitted to wards without an assigned pharmacist.

The ED pharmacists will collaborate with the interdisciplinary teams and perform the following tasks according to patients' and EDs' needs: medication history taking, MedRec, MedRev, drug therapy recommendations, guidance on drug administration, medication information and counselling to patients/next of kin and healthcare personnel and communication about medications and changes in medication regimes, see figure 3. Standardised procedures, such as the integrated medicines management methodology,[27] will be applied where possible. However, this is a complex intervention with a pragmatic approach where the intervention itself is not standardised, which better reflects the real-world setting. Inclusion of pharmacists in the team can lead to additional changes in the service when physicians and nurses use the pharmacists as a resource. Each patient will require different clinical interventions.[28] Therefore, how, when and which task will be performed for each patient cannot be predetermined, but must be decided based on patient's needs and time constraints. Thus, not every patient will

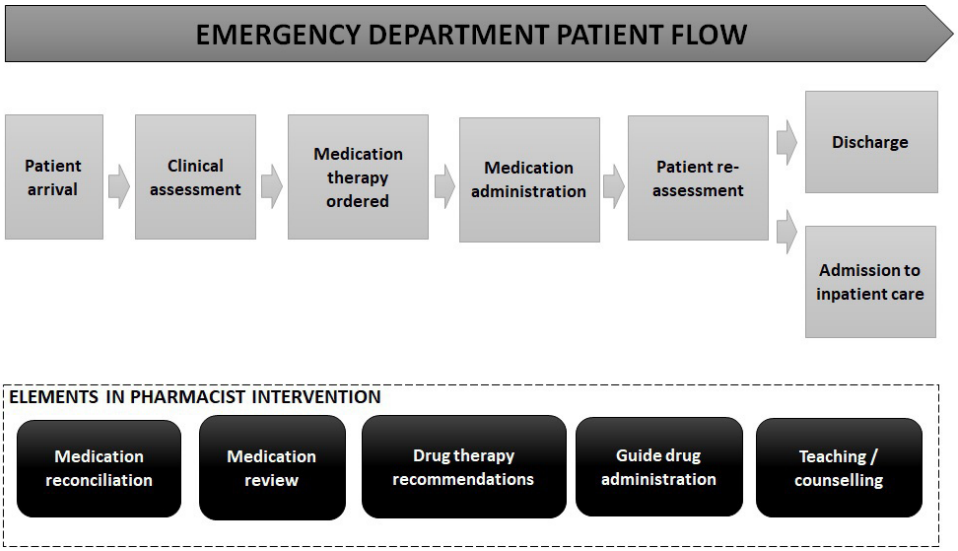

Figure 3 A pharmacist intervention in the emergency department (ED) put in the perspective of the ED patient flow.

receive the same intervention by the ED pharmacists, and not every nurse or physician would get discuss the same medication related issues with the ED pharmacists. The ED as a unit will be providing an extended service during the intervention period.

Preparing for the intervention

In order for physicians, nurses and pharmacists to prepare well for the intervention, we will introduce three initiatives that should ease the introduction of a new staff member; (1) information campaign to the EDs through emails, physical meetings and flyers, (2) theoretical and practical training of the clinical pharmacists in typical ED tasks in a fast-paced environment and (3) simulated ED team work with representative patient cases. The clinical pharmacists that are going to work in the EDs are trained as clinical pharmacists in other departments. In addition, they will go through a short training programme with lectures, seminars, discussions and observations, focusing on work flow in EDs and how the pharmacists may contribute.

Patient and public involvement

A patient representative has been involved throughout the whole duration of study planning period, already before application to funding was submitted. The one patient representative is member of a patient representative organisation where she, on a regular basis, discusses study-related issues with other patient representatives. More specifically, the patient representative is present at all project meetings where the whole project group is gathered to discuss study progress, design, research questions, outcome measures, patient inclusion and substudies (we are running substudies interviewing patients and healthcare personnel). We directly ask for advice on any aspects where patient perspectives are needed and she actively participates in discussions at all levels. As patients will not be asked for participation in this study, the patient representative has not been involved in patient recruitment. She is, however, involved in the patient information campaign and patient recruitment for the substudies. Except for scientifically result presentations, the study results will be disseminated to the study participants through public media, for example, newspaper articles or patient organisation presentations. The patient representative will play an important and active role in disseminating the results.

Outcomes

All outcomes below come from national registry data (the Norwegian Patient Registry and the cause of death registry).

Primary outcome

The primary outcome is 'time in hospital during 30 days after admission to the ED', which is a composite endpoint combining (1) time in ED during stay, (2) time in hospital during stay if hospitalised and (3) time in ED and/or hospital if rehospitalised within 30 days after each ED admission. This is an endpoint that has previously shown an effect in a Canadian study where pharmacist-led MedRev reduced time in hospital among high-risk patients under 80 years of age.[16]

Each patient can have more than one stay included in the study, but any admission during the 30-day time window after a previous admission will be excluded in order to avoid counting the stay twice, as an admission and a readmission in the previous stay. See figure 4 for a graphical representation of the inclusion and exclusion of stays.

Secondary outcomes

Time to rehospitalisation (unplanned)

We will measure time before the first unplanned rehospitalisation and compare the duration from the control period to the duration from the intervention period.

30-day rate for rehospitalisation (unplanned)

The 30-day rate for rehospitalisation during the control period will be compared with the trial period where ED pharmacists will be present in the ED. The rate will be measured by the number of patients who are rehospitalised within 30 days after their index stay.

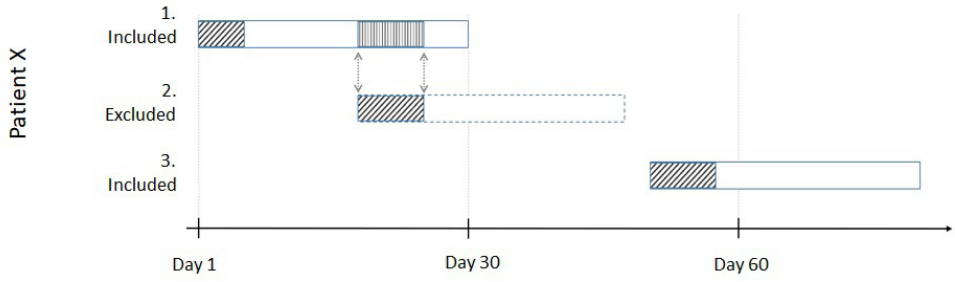

Figure 4 A graphical representation of the inclusion and exclusion of stays. Patient X is admitted on day 1 and stays in the hospital for 5 days (first box). The patient then gets admitted again on day 18 (second box) for another 7 days. These 7-day count towards the primary endpoint during the 30-day time window after the first admission. However, to avoid double-counting time, the second admission is excluded as a separate stay. The third stay (third box) is an admission on day 49 and it is counted a new stay with its own 30 days.

LOS in ED

The ED LOS will be represented in minutes as discharge time from the ED (or time transferred to a hospital ward) minus admission time in the ED.

LOS in hospital

LOS in hospital will be calculated as discharge date minus admission date.[29]

Mortality

We will measure mortality rate during 30 days after admission to the ED.

Sample size calculation

The total number of admitted patients per month is about 1300, 1000 and 500 in Tromsø, Bodø and Harstad, respectively. We assume that 20% will be missing complete registry data and will have to be excluded. This leaves us with 2240 admissions per month, 26 680 admissions in total. Of these patients, we anticipate that 15 360 admissions will occur during the intervention period.

Our primary outcome was previously applied in a Canadian study, where they showed a significant 0.5-day reduction the primary endpoint after a similar intervention.[16] If we assume a more conservative effect size of 0.25 days and a mean LOS in Norwegian hospitals of 4.2 days (SD=2)[30] we can calculate the required sample size using adjusting a for stepped-wedge design.[31] Using a significant level of 5% and power of 90% and an intraclass correlation of 0.001 (very little selection in who goes to the different EDs), we will need a minimum of 5222 admissions in each group.

Data collection and follow-up

We will collect data retrospectively from national health registries, patient records and hospital systems, see table 1. Study participants will be followed up for 3 months after each ED admission as described above. To adjust for long-lasting impacts, we will also collect data related to 6 months before and after each ED stay.

Statistics and data analysis

Data will be assessed for normality and analysed according to appropriate statistical distributions. The baseline demographic and clinical characteristics will be summarised using proportions, means and SD, or median and IQR, as appropriate. The reporting of results will follow the Consolidated Standards of Reporting Trials guidelines.[32]

Regression modelling will be used to adjust for potential confounders such as calendar time, this will be done using generalised estimating equations in order to accommodate the cluster nature of the data. Subgroup analyses based on variables such as age, gender and reason for visiting the ED will be done in order to study if any groups benefit more from our intervention. The main analysis will be done on all stays with an ED visit during the intervention time compared with all stays with a visit during the control period. The study statistician will be blinded to whether each individual patient visited the ED during the control or intervention period until the analysis is completed. All statistical tests will be interpreted with a significance level of 5% (two tailed).

Data from the study will also be used in other projects as described in discussion part.

Table 1 Overview of variables to be collected on patient and pharmacist level

Variable	Description	Data source	Timing/time interval
Demography and patient information	Year of birth, community, sex, place of stay, NPR number, comorbidities	NPR EPJ	Retrospective
Stay in ED	Hospital, triaging, time in, time out, site for discharge, admission diagnoses (tentative and established)	NPR EPJ	Retrospective 6 m. before and after ED visit*
Mortality	Mortality within 30 days after ED index stay and cause of death	NPR CDR	Retrospective 6 m. before and after ED visit*

*A larger period than the primary endpoint in order to adjust for long-lasing impacts in the analyses.
CDR, cause of death registry; ED, emergency department; EPJ, electronic patient journal; m, months; NPR, Norwegian Patient Registry.

Ethics and dissemination

The study has been approved by the Patient Protection Officer at the Hospital Pharmacy of North Norway Trust and the three involved hospitals. The trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice and the Declaration of Helsinki. Since our intervention will be implemented as a part of standard practice, patient consent will not be necessary. However, patients will be informed about the ongoing study on a general basis in all EDs with ads on TV screens, posters and flyers. Patients will have the opportunity to actively refrain from study participation, and information about how to do this will be easily available. The retrospective data collection from national registries has been approved by the Regional Committees for Medical and Health Research Ethics and local Patient Protective Officers at each hospital.

We aim to publish study results in international peer-reviewed open access journals, at national and international conferences and in local, national and international media.

DISCUSSION

This intervention study is a part of an overarching project 'pharmacist in the ED' with an overall aim to investigate the impact of the ED pharmacist implementation on several aspects, not only patient safety outcomes. Consequently, a wide range of studies will be performed in addition to this intervention study, and data from the intervention study will also be applied to other studies. We will identify barriers for including the ED pharmacists and identify how the ED pharmacists should be working. We will apply interviews and observations in the EDs, to identify if the intervention will have an effect on primary care services. We plan to investigate if rate of visits to GPs are influenced. Also, we will investigate how medication regimes are influenced by the ED pharmacist intervention. Medication appropriateness will be determined through a systematic comparison of medication appropriateness in the intervention group compared with the control group. The medication appropriateness index is a possible tool.[33] We want to identify which are specific pharmacy services and recommendations delivered by the ED pharmacists by applying journal data documented in the electronic patient journals (EPJ). The data on these interventions will be retrospectively collected from the EPJ and the interventions will be categorised into different activities (eg, MedRec, MedRev, patient counselling). The DRPs will be identified and outcomes after discussion with the interdisciplinary team registered. The clinical relevance of a randomly selected part of the interventions will be retrospectively evaluated by an expert team. We will explore the acceptance rate of pharmacist recommendations, which may be applied as a proxy for the clinical relevance of the recommendations made by ED pharmacists. We will also investigate whether the rehospitalisations in the study population are drug related. This may be done by applying expert groups and the Delphi methodology for agreement, or by applying the assessment tool for identifying Hospital Admission Related Medications 10.[34] We aim to study whether the health-related quality of life (HRQoL) is influenced by the intervention. We will select a small and random part of the study population who will be asked to participate in an HRQoL study, where the EQ-5D VAS (Visual Analog Scale) tool will be applied.[35] We will also investigate the cost-effectiveness of the intervention, a health economic simulation model evaluating the cost utility of the ED intervention will be developed. The simulation will compare future health of patients in two strategies; either with the ED pharmacists or with the current practice, with no pharmacists. Data from the other studies will be applied in the cost-effectiveness study.

This is the first study located in the literature testing a pragmatic real-world pharmacist approach, including all patients going through the ED throughout a whole year. Results will give valuable insight into outcomes of ED pharmacist involvement, and positive results may add speed to the implementation of pharmacists in ED settings world-wide. The main strength of the study is the stepped-wedge design, allowing for inclusion of the total population going through the ED in the study period. Another strength is the unbiased endpoint data collection from high-quality national registers. Some limitations do, however, exist, the main one being the inclusion of the pharmacists in the ED team. If they are not properly included, they may not be able to fully perform pharmacist services and consequently not able to influence patient care. Regarding generalisability, we believe results may have implications for both Norway, Scandinavia and other countries with a similar ED and hospital structure.

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Contributors RE, RV, KS and BHG were involved in the study design. RE, RV, KS and BHG drafted the manuscript. ECL, EHO, TJ, BZ-H, TR, TW, LR, OMF, P-CV and HMF read and commented on the draft. All authors read and approved the final manuscript.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	11
Funding	#4	Sources and types of financial, material, and other support	11
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	11

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	11
Roles and responsibilities: sponsor and funder	#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	11
Roles and responsibilities: committees	#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)	11
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	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
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, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	5

		be collected. Reference to where list of study sites can be obtained	
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)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#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)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
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)	5
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	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	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	5
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	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection plan	#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.	8

		Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#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	9
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	9
Statistics: outcomes	#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	9
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
Statistics: analysis population and missing data	#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)	9
Methods: Monitoring			
Data monitoring: formal committee	#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	10
Data monitoring: interim analysis	#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	9
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events	11

		and other unintended effects of trial interventions or trial conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	10
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)	11
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
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	10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
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	11
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the	10

		public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	11
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	11