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.

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. It 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.

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% and increased appropriate use of antimicrobials with almost 80% acceptance rate of pharmacist recommendations. Seven of twelve trials in a review by Kaboli et al reported on reduction of DRPs and medication errors. In fact, studies indicate that more than 80% of DRPs can be identified and solved with clinical pharmacist...
interventions. Studies also show reduction in hard and costly endpoints such as hospital utilisation, 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.

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%, reduced medication omissions and delays, 12-hour shorter hospital stays per patient, reduction in rehospitalisation by 5%, and decreased mortality rates. There is a wide range of services provided by clinical pharmacists in the ED that has shown an effect in various countries and settings.

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. 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). 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. 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.

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 (Bodo, 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
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...
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 3 A pharmacist intervention in the emergency department (ED) put in the perspective of the ED patient flow.
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, 26680 admissions in total. Of these patients, we anticipate that 15360 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.

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

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

*A larger period than the primary endpoint in order to adjust for long-lasting impacts in the analyses.

CDR, cause of death registry; ED, emergency department; EPJ, electronic patient journal; m, months; NPR, Norwegian Patient Registry.
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. 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 drafted the manuscript. ECL, EHO, TJ, BZ-W, 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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Disclaimer The sponsor has no part in collection, management, analysis and interpretation of the data, as well as writing and reporting study conclusions.

Competing interests None declared.

Patient consent for publication Not applicable.

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Supplemental material

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REFERENCES

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 SPIRIT reporting guidelines, and cite them as:


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<td>Roles and responsibilities: sponsor and funder</td>
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<tr>
<td>Roles and responsibilities: committees</td>
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</tr>
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**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

<table>
<thead>
<tr>
<th>Eligibility criteria</th>
<th>#10</th>
<th>Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)</th>
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<td>Interventions:</td>
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<tr>
<td>description</td>
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<td>Interventions for each group with sufficient detail to allow replication, including how and when they will be administered</td>
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<td>Interventions:</td>
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<td>modifications</td>
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<td>concomitant care</td>
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<td>Participant timeline</td>
<td>#13</td>
<td>Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)</td>
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<td>Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations</td>
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<td>Recruitment</td>
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<td>Strategies for achieving adequate participant enrolment to reach target sample size</td>
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### Methods:
**Assignment of interventions (for controlled trials)**

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<th>Description</th>
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<td>Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.</td>
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<tr>
<td><strong>Allocation concealment mechanism</strong></td>
<td>Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned.</td>
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<td><strong>Allocation: implementation</strong></td>
<td>Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions.</td>
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<tr>
<td><strong>Blinding (masking)</strong></td>
<td>Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how.</td>
</tr>
<tr>
<td><strong>Blinding (masking): emergency unblinding</strong></td>
<td>If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial.</td>
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### Methods: Data collection, management, and analysis

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Data collection plan</strong></td>
<td>Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known.</td>
</tr>
</tbody>
</table>
Reference to where data collection forms can be found, if not in the protocol

Data collection plan: retention

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

Data management

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

Statistics: outcomes

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

Statistics: additional analyses

Methods for any additional analyses (eg, subgroup and adjusted analyses)

Statistics: analysis population and missing data

Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring: formal committee

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

Data monitoring: interim analysis

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

Harms

Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events
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

Ethics and dissemination

Research ethics approval #24 Plans for seeking research ethics committee / institutional review board (REC / IRB) approval

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)

Consent or assent #26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

Consent or assent: ancillary studies #26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

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

Declaration of interests #28 Financial and other competing interests for principal investigators for the overall trial and each study site

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

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

Dissemination policy: trial results #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

Dissemination policy:

**authorship**

#31b  Authorship eligibility guidelines and any intended use of professional writers

Dissemination policy:

**reproducible research**

#31c  Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

**Appendices**

Informed consent materials

#32  Model consent form and other related documentation given to participants and authorised surrogates

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

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