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Improvement of perioperative care of the elderly patient (PeriAge): protocol of a controlled feasibility study

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ABSTRACT

Introduction Geriatric patients have a pronounced risk to suffer from postoperative complications. While effective and risk-specific pre- and intraoperative measures have been well studied in controlled research settings, they are rarely found in routine healthcare. This study aims (1) to implement a multicomponent pre- and intraoperative intervention for elderly patients and investigate its feasibility and (2) to assess the effectiveness of the intervention in routine healthcare.

Methods and analysis Feasibility and effectiveness of the intervention will be investigated in a monocentric, prospective, non-randomised, controlled trial. Data will successively be collected from control, implementation, and intervention group. Patients aged above 64 with impending surgery minimum 5 days after a premedication appointment will be included. A sample size of 240, n=80 per group, is planned. Assessments will take place at inclusion and 2, 30, and 180 days after surgery. Analyses are performed using a mixed-methods approach. The effectiveness will be assessed using mixed segmented regressions. The primary endpoint is functional status. Secondary endpoints include cognitive performance, health-related quality of life, length of inpatient stay and occurrence of postoperative complications. Feasibility will be assessed (a) through qualitative semi-structured interviews with clinical staff and patients and (b) quantitative analyses of the data quality, focussing on practicability, acceptance, adoption, and fidelity to protocol.

Ethics and dissemination The study will be carried out in accordance with the Helsinki Declaration of the World Medical Association and to principles of good scientific practice. The Ethics Committee of the Medical Association Hamburg, Germany approved the protocol (study ID: PV5596). Results will be disseminated in scientific journals and presentations at healthcare conferences.

Trial registration ClinicalTrials.gov Identifier: NCT03325413.

Keywords feasibility, perioperative care, elderly, geriatric anaesthesia, anaesthesiology, post-operative complications, complex interventions, instrumental activities of daily life, quality of life, patient-reported outcomes, process evaluation.

Strengths and limitations of this study

+	Effectiveness AND feasibility evaluation of a multicomponent pre- and intraoperative intervention under real-life circumstances for a variety of surgeries and with few inclusion restrictions.
+	High patient relevance due to the use of a wide range of patient-reported outcome measures and long term follow-up
+	Capturing multidisciplinary experience from anaesthetists, medical assistants, nurses, and patients.
-	Difficulties to implement and control for all intervention components adequately due to real-life circumstances.
-	Risk of selection and attrition bias due to the non-randomized design and selective dropout.

INTRODUCTION

In Germany, every second inpatient surgical procedure is performed on patients aged 65 years and above.[1] This cohort has an elevated risk to suffer from a range of postoperative complications (POCs).[2-6] These include postoperative delirium (POD), pulmonary infection, cardiovascular events and an overall higher rate of postoperative morbidity, consequentially extended hospitalisations, and mortality, but also long-term general decline of health, cognition, functional status, and quality of life after surgery.[7-11] Further, immediate POCs can result in and amplify long-term decline of health and long-term loss of functional independence and quality of life. The most common patient-related risk factors are a reduced functional status, (i.a. sensory and cognitive impairment, poor physical fitness and mobility, malnutrition, polypharmacy, and multi-morbidity).[12-15] Treatment-associated risk factors include excessive fasting prior to surgery, dehydration, disorientation, disturbed sleep-wake-cycle, potential-inadequate medication, anxiety, mental overload and -stress, pain, hypothermia, loss of sensory orientation during in-patient stay,[16] and high invasiveness of the anaesthetic procedures and surgery (see figure 1).

[FIGURE 1]

In order to reduce POCs and generally improve clinical outcomes in elderly patients, it is important to detect patient-related risk factors prior to surgery and implement appropriate prophylactic measures. Accordingly, risk-specific prehabilitative interventions need to find their way into routine healthcare[12]. Evidence is consistent, that preoperative prehabilitative measures can reduce the postoperative risk suffering POCs for elderly patients, and hence improve long-term functional status. Protective measures include countering malnutrition,[17,18] poor physical fitness,[19,20] and enhancing breathing exercise techniques,[21] as well as reducing potentially inappropriate or multi-medication.[22,23] Handling of preoperative fasting is another problematic aspect of perioperative care. While guidelines support that 6 hours of preoperative fasting are sufficient in most cases, this is hardly met in clinical practice.[24,25] Recent studies, however, point out the protective effect of preoperative carbohydrate intake and hence glucose reserve on the postoperative outcome, especially in vulnerable patients.[26] Further risk factors for less favourable postoperative outcomes are anxiety and psychological and mental stress. While the necessity of an inpatient surgery alone provokes a stress reaction, so does the entire medical procedure, from preanaesthetic evaluation to inpatient discharge. The unfamiliar environment and the uncertainty of the outcome can amplify anxiety and stress. This holds particularly true for potentially vulnerable patient groups, as is the geriatric cohort. Stress is well established to negatively impact somatic and mental health outcomes.[27] However, loss of orientation and high levels of stress can be reduced by marginal changes in routine preoperative procedures. Patients can be re-oriented by retaining glasses and hearing aids up to the anaesthetic induction, and by reducing mental

stress and overload. This can be done by ensuring that the patient understands the procedures for surgery and therapy and by encouraging the presence and involvement of relatives,[28] which in turn may lead to a higher preservation of preoperative self-reliance and health-related quality of life.[29] While the risk of suffering somatic POCs is increased in patients, who have blood deficiency states and undergo sanguineous surgery, this risk can be reduced by individualised iron substitution.[30-33]

Further, the risk of different intraoperative procedures should be taken into consideration. It is recommended to monitor the depth of anaesthesia using e.g. bispectral index (BIS) analysis, as deep anaesthesia is associated with a higher incidence of postoperative delirium.[34] Postoperative pain is a predisposing factor for POCs.[35] To enable sufficient postoperative, opioid-saving analgesia, the use of catheter-assisted regional anaesthesia is preferable for elderly patients.[32,36]

While these risk factors are well studied and several intervention components have been shown to reduce complication rates in controlled research settings,[37-39] many effective intervention components are not used in routine care,[40,41] as both an extensive preoperative risk assessment and the administration of pre- and intraoperative measures are time-consuming and costly.

To improve the geriatric patient's postoperative safety and health, the preanaesthetic evaluation needs to be updated to the current state of research of risk- and preventive factors. Feasibility and benefit of an extended preanaesthetic evaluation and the ensuing administration of corresponding prophylactic interventions need to be demonstrated, in that it is possible to improve the pre- and intraoperative care of geriatric patients with feasible effort, leading to an overall reduction in long-term physical and cognitive complications as well as a reduced hospitalisation period.

Objectives In this study, a demand- and risk-based intervention (called PeriAge-intervention) is developed and implemented into routine healthcare.

Objective (1) is to assess and provide first evidence of the effectiveness of the PeriAge- intervention, improving the postoperative outcome of a sample of elderly patients at a university hospital in Germany. The primary outcome is the change in the autonomous functioning six months after surgery, measured via the Instrumental Activities of Daily Living (IADL, Lawton and Brody, 1969). The corresponding primary hypothesis is that individualized care of the patient as part of the PeriAge intervention enhances postoperative autonomy in comparison to the control group. We expect a smaller reduction of the IADL score in the experimental condition after one and six months. Additionally, we will test the composite effect of the PeriAge intervention on POCs, cognitive performance, length of inpatient stay, and several patient-relevant outcomes elaborated below.

Objective (2) of our study is to investigate the feasibility[43] of the PeriAge intervention, specifically its implementation and realisation in ongoing hospital operations. We intend to show that it is possible

to implement a multidimensional intervention into routine care and identify main challenges of implementation. The feasibility of the implementation is categorised after the elements practicability, acceptance, adoption, and fidelity to protocol.

METHODS AND ANALYSIS

Study design The PeriAge intervention will be evaluated in a monocentric, non-randomized, controlled study. The study consists of three successive arms, each six months in lengths (see figure 2), while lengths of arms remain subject to extension as required. Patients will be allocated in a predefined order; the project starts with the usual routine healthcare as control, followed by the implementation phase and concluded by the intervention phase. Simultaneous to the control phase, the individual components of the PeriAge intervention will be elaborated, and their implementation prepared. The implementation phase is used to implement the PeriAge intervention into routine care gradually, leaving space for adoption, tailoring, and modifications as necessary. With the start of the intervention phase onwards, the final PeriAge intervention will be administered and information of its feasibility will be gathered. The 3-year mixed-method project comprises two simultaneous branches, evaluating the feasibility and effectiveness of the PeriAge intervention, respectively.

Study population Participants are patients aged above 64 with impending elective surgery in a university hospital of a German metropolitan region. In order to test the PeriAge intervention with high external validity, patients receiving all types of surgeries except for neurocerebral- and ophthalmologic surgeries will be included. While cognitive performance and functional status cannot be independently attributable to the interventions after neurocerebral surgeries, ophthalmologic surgeries take place at an external site within the university medical centre and execution of intraoperative interventions cannot be guaranteed. Exclusion criteria are emergency surgery, surgery within five days of indication, and surgery with planned postoperative intensive care or planned postoperative hospitalisation for fewer than 24 hours. Further, patients will be excluded who are analphabetic, who do not have sufficient command of the German language and patients who suffer from psychosis, illicit drug use, chronic use of benzodiazepines, and patients who suffer from an incorrigible auditory or visual disability.

Effectiveness assessment of the PeriAge intervention and its influences

Procedures and instruments

Within each arm, the study follows a pre-post design. Patient assessments take place once before intervention initiation and at three time points after intervention completion as shown in figure 2. All patients will undergo an extensive preanaesthetic evaluation (T0). In addition to the routine check-up, the assessment entails brief neuropsychological testing to evaluate the patient's cognitive state,

strength and mobility testing and patient-reported outcome measures (PROMs) about somatic and mental health, current living situation and quality of life. Additionally, the responsible anaesthetist will record malnutrition (see table 1), demographics and the need for sensory aids. In the implementation and intervention group, the PeriAge intervention will be introduced.

Table 1. Multidimensional perioperative assessment; instruments, type and time point of enquiry and direction of hypothesised effect.

Domain	Instrument	Operationalisation	Time point				exp. direction of effect**
			T0	T1	T2	T3	
Social, physical and autonomous functioning	IADL*	functional status	x		x	x	↑
	Social situation by Nikolaus[44]	social status	x				N/A
	LUCAS-FI	frailty proxy	x		x	x	↓
	MNA-SF	malnourishment	x				N/A
	1 minute sit to stand test[45,46]	mobility	x		x	x	↑
	Timed up & go test[47]	physical strength, stamina	x		x	x	↑
	vigorometer (hand force)[48]	physical strength	x	x	x	x	↑
orientation & cognition	CAM-ICU	delirium		x			↓
	DemTect	cognitive functioning	x	x	x	x	↑
	TAP alertness subtest		x	x	x	x	↑
	TMT		x	x	x	x	↑
	Subjective cognitive rating	sense of cognitive functioning	x	x	x	x	↑
quality of life & mental health	SF-12[49]	health-related quality of life	x		x	x	↑
	GDS	depressive symptoms	x		x	x	↓
	GAD-2	anxiety symptoms	x		x	x	↓
somatic POCs	POSPOM	Postoperative mortality risk scoring	x				N/A
	Patient blood management†	Deficiency states (Hb, Transferritin, Ferritin)	x				
	EPR†	somatic complications (incl. mortality)		x	x	x	↓
		length of hospitalisation		x			↓
	history assessment	polypharmacy	x				N/A

POC: post-operative complications. **IADL:** Instrumental Activities of Daily Living. **LUCAS-I**: Longitudinal Urban Cohort Age Study - Instrument (Dapp, Anders, von Renteln-Kruse, et al., 2012). **MNA-SF**: Mini Nutritional Assessment - Short From (©Nestlé Nutrition Institute, 1993). **CAM-ICU**: Confusion Assessment Method for Intensive Care Units (Ely, Margolin, Francis, et al., 2001). **DemTect**: Dementia Detection (Kalbe, Kessler, Calabrese, et al., 2004). **TAP**: Test battery for attentional performance (Zimmermann and Fimm, 1993). **TMT**: Trail Making Test (Reitan and Wolfson, 1992). **SF-12**: Short Form health survey (Bullinger and Kirchberger, 1998). **GDS**: Geriatric Depression Scale (Yesavage, Brink, Rose, et al., 1982). **GAD-2**: Generalized Anxiety Disorder 2 (Spitzer, Kroenke, Williams, et al., 2006). **POSPOM**: Preoperative Score to Predict Postoperative Mortality (Le Manach, Collins, Rodseth, et al., 2016). **EPR**: electronic patient record; *primary effectiveness outcome, all instruments that are administered at T3 and the CAM-ICU will be interpreted as secondary outcomes; † does not fit the description of an instrument, but is listed here for completeness; **the expected effect refers to the comparison between control and intervention group. An up-pointing arrow connotes a reduced respective decline in the intervention group, not more favourable outcomes postoperatively.

[FIGURE 2]

The first postoperative enquiry takes place (T1) within the first few days after surgery. At that point, delirium,[52] cognitive functioning,[53-55] physical strength,[45,48] and mobility[46] are assessed and information about somatic complications is extracted from the hospital's electronic patient record (EPR). POD is

screened for using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) including modified Richmond Agitation and Sedation Scale (m-RASS) in the first five days following surgery according to guideline recommendations.[60] T2 and T3 take place one and six months after surgery respectively.

Short-term outcomes are anaesthesia duration, duration of inpatient stay and the occurrence of somatic postoperative complications, including delirium and mortality. PROMs and a brief neurocognitive assessment, evaluating patient's postoperative cognitive abilities will be used as parameters to assessing long-term effects of the intervention, one and six months after surgery. PROMs are used to assess functional status, a proxy for frailty, health-related quality of life, and mental morbidity; the neurocognitive assessment focusses on alertness, cognitive flexibility, and working memory. See *table 1* for instruments, operationalisation, time point of assessment and expected direction of effects.

The proposed intervention components affect either the pre- or the intraoperative phase. While all intervention components shall counteract POC and decline of autonomy one and six months after surgery, the specific measures focus on different aspects of postoperative health. Special attention is given to everyday functioning; including nutritional and fitness status, orientation, and somatic complications (see figure 1). Malnourished patients will be provided with high-protein drinks for a maximum of 14 days up to the eve of their surgery day. Additionally, patients are offered a carbohydrate drink two hours prior to surgery to forestall potential glucose depletion,[61] but also to reduce preoperative anxiety and discomfort.[62] Patients with poor physical fitness are prompted to undergo preoperative progressive strength and fitness training, instructed via a short personal introduction and information brochures and logged by a self-report diary. All patients are suggested performing breathing exercises, taught by an information brochure.

Interventions

Intervention components to reduce mental overload and prevent disorientation comprise the inclusion of relatives, extensive information giving about planned procedures, and the preservation of sensory orientation. The systematic inclusion of relatives or significant others in all procedures from the beginning of the inpatient stay onwards shall counteract potential disorientation within the unfamiliar, and potentially highly stressful setting. A detailed and comprehensible pre-operation discussion including information about the inpatient stay and the scheduled POC prevention measures shall serve as an additional orientation aid. Patients will be encouraged to bring personal items at admission, such as pillows, photographs, and music. This shall support recognition and diminish the risk of suffering POD. Furthermore, patients with need for vision aids, acoustic instruments, and dental

prostheses are encouraged to retain these aids up to the anaesthetic induction to foster sensory orientation.

Measures to prevent somatic complications consist of screening and potential adjustment of potentially inadequate or multi-medication in accordance with national and international recommendations[22,23] and general refrainment from administering benzodiazepines. Patients with anaemia will be screened for iron deficiency. If an iron deficiency anaemia is diagnosed and the risk for intraoperative bleeding is estimated to be above 10%, patients will be supplemented with intravenous iron prior to surgery in accordance of the principles of Patient Blood Management.

The proposed intraoperative measures shall prevent somatic complications and mental disorientation. The geriatric anaesthesia concept includes employing regional anaesthesia alone or in combination with general anaesthesia whenever possible to ensure an opioid-saving postoperative analgesia regime. When general anaesthesia is performed, BIS is used for neuromonitoring purposes. Further, certain medications will be avoided intraoperatively, in particular, benzodiazepines, atropine, anticholinergics, and central alpha-agonists. If muscle-relaxants are needed, short-acting substances are preferred as well as postoperative catheter-assisted analgesia. Thermal blankets from anaesthesia induction to post anaesthesia care will be given to the patient in order to avoid hypothermia. See figure 1 for a comprehensive list of pre- and intraoperative risk-specific interventions.

During the implementation and intervention phases, training events by study staff and external experts will be performed at every affected hospital ward and in anaesthesia meetings. These meetings inform about relevant topics of in-patient care such as the preoperative administration of carbohydrate drinks, measures of POD prevention, patient information and adequate postoperative analgesia in the elderly. Anaesthetists are instructed to follow the comprehensive administration of the BIS in surgery.

Recruitment/sample size

The required sample size is based on sufficient power for identifying rare foreseen and unforeseen incidents, as suggested for feasibility trials.[63] The emergence of POCs depends on underlying conditions and type of surgery conducted. In the elected cohort, the likelihood of an occurrence of POCs is considerably above 10%,[64,65] so is the risk of losing the level of preoperative functioning and autonomy. A sample size of 30 is minimally required for the identification of an event with an average occurrence of 10% with a confidence of 95%.[63] Because of an expected dropout greater than 30%, as is common in studies that are performed under routine conditions, together with the plan to analyse multiple outcomes, we aim to recruit 80 patients in each of the three study arms, resulting in approximately 240 patients in total.

Data analysis

We plan to use the intention to treat (ITT) method to conduct the primary analyses. Missing values will be accounted for by using mixed modelling techniques. The data will be analysed using descriptive and inferential statistics. The effects of the intervention will be estimated by using segmented regressions.[66-68] For the effectiveness analyses, generalised two-level regression models (linear, logistic or Cox depending on the outcome) will be used. This enables a nuanced estimation of time- and intervention effects, taking into account time trends within- and between the groups. The first level connotes the progression of the individual patients and will be estimated in intercept and slope. The second level connotes the difference between persons, taking into account time and group-effects. Should the assumptions for segmented regressions be violated, the models will be adjusted accordingly. Propensity score methods will be used in case of strong violation.[69] Results with $p<.05$ will be considered as statistically significant. As this study is of explorative nature, no adjustments will take place for multiple testing. However, the elevated risk of an occurrence of type-I errors will be regarded when interpreting the results.

Feasibility assessment of the implementation

Procedures and instruments

A process evaluation is conducted to explore the feasibility of the PeriAge intervention. The critical elements for capturing the degree of feasibility in this study are acceptance of those affected, in particular patients and clinical staff, as well as the, practicability, realisation and adoption, accessibility of the intervention, and fidelity to protocol, chosen by means of the current standards of feasibility studies (see table 2).[70-72]

Table 2. Quantitative and qualitative feasibility assessment; type and description of analysis.

Domain	Operationalisation	Quantitative analysis	Qualitative analysis***	
		Brief description	Staff	Patient
Acceptance	Satisfaction with the intervention and its implementation	--	x	x
Practicability	Relevance of the intervention and compatibility with the specific setting	(Effectiveness outcomes, see above)	x	x
Realisation and adoption	Realisation: intend and action to employ the intervention Adoption: adjusted execution of the intervention to fit the setting and recording of these adjustments	- Data quality analysis on congruency, completeness, plausibility, and sources of potential errors. → reported and adapted if necessary - descriptive statistics of self-report diary and intervention checklist	x	

Accessibility	Penetration of intervention and access for all designated and eligible recipients	Evaluation of reasons for non-participation, recruitment progression and attrition rate Analysis of demographics and morbidity of dropouts	x
Fidelity to protocol	Quality and of intervention delivery and adherence to implementation protocol	Evaluation of implementation processes and interim adaptations by intervention checklist records	x

***Thematic analysis evaluation of semi-structured interviews

Using a mixed method approach, the feasibility evaluation is segmented into a quantitative and a qualitative analysis. The quantitative analysis consists of continuous documentation of the realisation of the intervention from the implementation phase onwards (see figure 3).

[FIGURE 3]

An intervention checklist is filled in for every patient. This checklist is tailored on risk factors and interventions of the study and enquires about the proper execution of individual interventions e.g. the reduction of inappropriate polypharmacy, the retainment of orientation aids and the usage of the BIS during surgery. With this collection of process data deviations from the protocol can be prevented, or alternatively, detected. Additional plausibility analyses of the outcome data are performed.

For the qualitative feasibility analyses, information on the experience of the clinical and study staff and patients regarding the individual intervention components are collected and evaluated. Firstly, meeting logs of the project will be described. Secondly, semi-structured interviews will be conducted examining experience and opinion of the interviewee about adequacy and purpose of the intervention, as well as impediments and facilitators of the implementation process. The interviews will contain mainly open-ended questions. Interviewing patients and professionals of different contexts shall capture different perspectives on the implementation and increase the validity of the results. While the patient interviews will be held within the intervention phase after completing the T3 enquiry, the staff interviews will be conducted twice; once during the implementation phase and once after the termination of the intervention phase. The first staff interview serves not only as an inspection of feasibility, but also allows that necessary adjustments might be exposed and realised. The second interview repeats and finalises the inspection of feasibility.

Recruitment/sample size

Additional to the recruitment of 240 patients for the effectiveness analysis, it is planned to interview 5 to 10 study staff members medical assistants and clinicians, who are affected by the implementation. Additionally, seven randomly chosen patients of the intervention phase will be interviewed. These interviews take place after T3. The chosen sample size is based on experience and literature on saturation of information gain.[73]

Data analysis

To perform the process evaluation, two structured analyses of the process- and outcome data will be performed on congruency and completeness in order to detect potential discrepancies between conception and realisations. The first analysis is conducted before initiation of the implementation phase and the second is conducted after the data collection is completed. The results of the evaluations as well as the results of the intervention checklist (see above), will be examined via descriptive statistics. The interviews will be recorded, transcribed and analysed by using a realist thematic analysis approach,[74] specifically a framework content analysis.[75] The thematic analysis approach is a method by which qualitative data is coded into themes (see figure 4). We will use a mainly deductive approach, as our feasibility outcomes are already pre-defined (see table 2). Coding schemes are developed beforehand and discussed regularly. Nevertheless, we are open to the possibility of inductive theme generation, if data suggests. The results will be reported using consolidated criteria for reporting qualitative research (COREQ).[76]

[FIGURE 4]

Patient and public involvement Patients and public were and will not be directly involved in the research study design. However, within the qualitative analysis, we will assess the patient's opinion of the PeriAge intervention, and about burden and time required to take part in this study. One research question is dedicated to obtain and integrate the patient's opinion into the results and eventually into the decision whether to continue and incorporate the programme in routine care. It is not planned to involve patients in the dissemination of the results. If the intervention shows to be feasible and brings added value into the healthcare of geriatric patients, it will be maintained and expanded to all wards and all surgical geriatric patients in the university medical centre Hamburg-Eppendorf.

Software Microsoft Access will be used for data collection, storage, and preparation. For most quantitative data analyses, it is anticipated to use the software R[77] and IBM SPSS Statistics[78]. Lastly, the software MAXQDA[79] will be used for qualitative data analyses.

ETHICS AND DISSEMINATION

Ethical and safety considerations The study will be carried out according to the Helsinki Declaration of the World Medical Association. The principles of good scientific practice will be followed. Study participation is voluntary and may be withdrawn at any moment. Written informed consent will be obtained prior to participation. Patients will be fully educated about the aims and procedure of the study, data collection and the use of collected data. The rejection of participation has no negative consequences for patients and their care. No foreseeable risk at any moment results from the participation in this study. No compassionate use will be carried out. All intervention components are

non-invasive expect for the preoperative iron infusion if required according to the Patient Blood Management protocol. However, this is no experimental therapy method but an established and evidence-based measure, which is executed according to existing guidelines and approved by the local ethical review committee. Preserving principles of data sensitivity, data protection, and confidentiality requirements will be met. Significant deviations from the protocol, concerning recruitment, inclusion criteria, intervention, or statistical data analysis will be justified and discussed. Modifications and amendments will be listed in the appendices of the main publication. SPIRIT reporting guidelines have been used to write protocol.[80]

Dissemination plan The results of the project will be published in scientific journals. In order to assure high accessibility, we aim to publish our work in open access journals, conditions permitting. Furthermore, the results will be presented at relevant national and international conferences. Additionally, a data basis shall be created that will help to inform clinical practice guidelines that enable and improve perioperative care and surgical outcomes of geriatric patients, respectively.

Data deposition The collected data will be deposed on a protected server of the University Medical Centre Hamburg-Eppendorf, with strongly regulated access even for study personnel. Due to substantial obstacles to de-identification (relatively small sample, routine care, a large amount of qualitative data, etc.), individual participant data will not be shared publicly. Researchers who submit a methodologically sound proposal to the principal investigator that is approved by the responsible review committee will be allowed to use data.

AUTHORS CONTRIBUTORS

CO, MH, RK, and LK conceptualised the study, wrote the grant proposal, and obtained funding. LL, CO, AM, and LK designed the details of the study, with substantial contributions from MH and RK. RK is the responsible primary investigator of the project. LL and CO prepared the first draft of the manuscript. LP substantially contributed to implementing the individual interventions and the recruitment of patients. AEG and CZ, heads of the UKE Anaesthesiology department, supported and enabled the realisation of the study with their overall supervision. All authors contributed to critically revising the manuscript for important intellectual content, gave final approval of the version to be published, and agree to be accountable for the work as guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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approved the study design during the grant application process. It had no role in the conduct of the study and the publication process.

Competing interests None declared.

Patient consent Not required.

Ethics approval Ethics Committee of the Medical Association Hamburg, Germany (study ID: PV5596).

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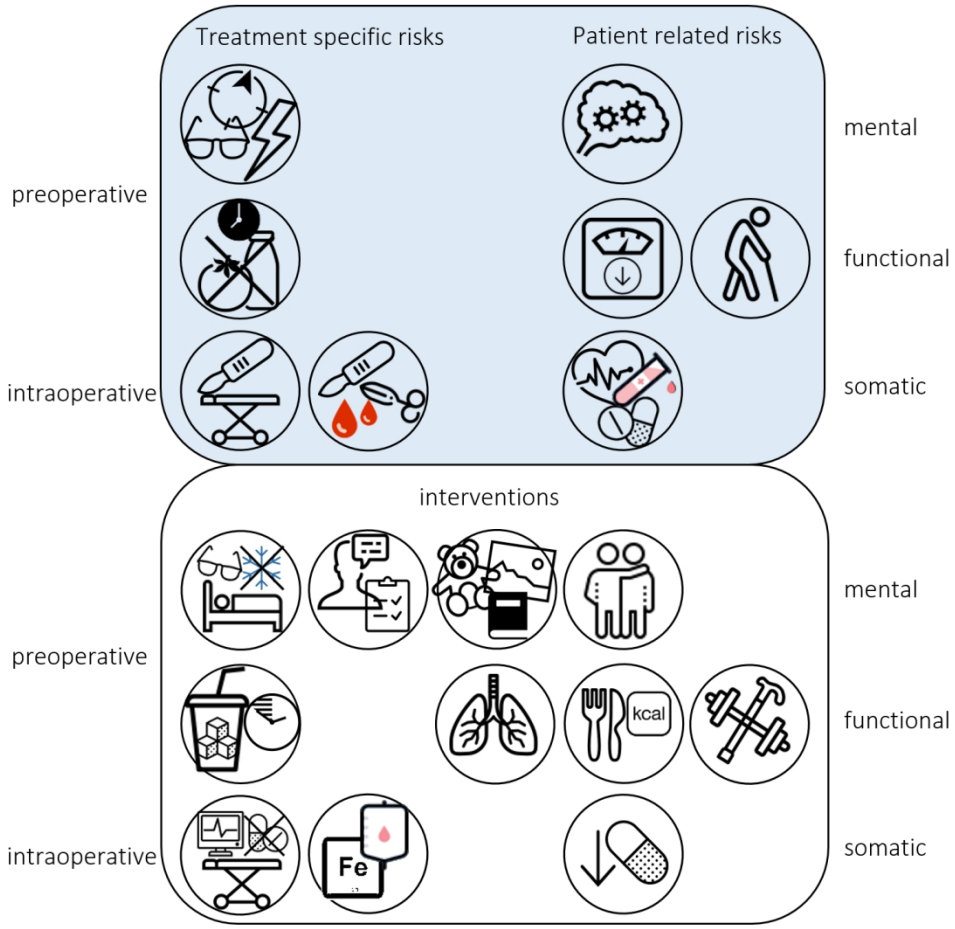

Figure 1. Age- and treatment related risk factors for developing POCs after surgery. In this study, these factors will be screened for in the preanaesthetic evaluation and corresponding preventive interventions will take place perioperatively if required and possible. Icons are used with permission from ©2018 Icons8 LLC, https://icons8.com/).

270x263mm (150 x 150 DPI)

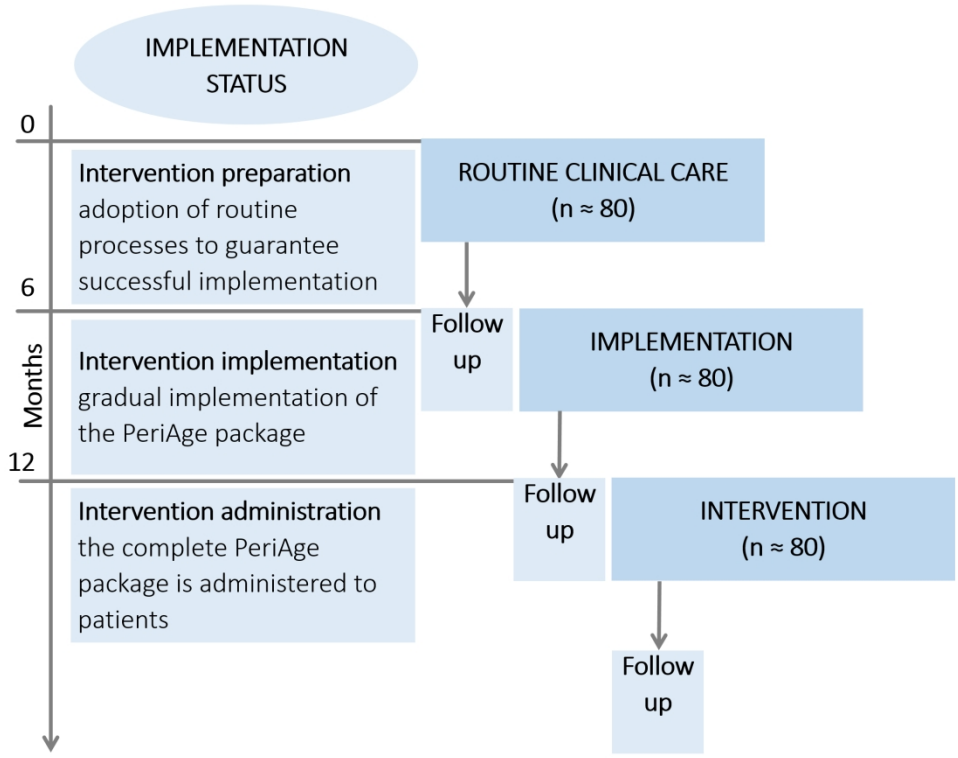

Figure 2. Sequential study design. Allocation randomisation is not feasible, due to the risk of contamination or cross over between groups. During the control and implementation phase, the intervention components will be developed, the implementation planned and gradually introduced. In the intervention phase, the exhaustive intervention will be applied. The enquiry period, entailing recruitment and follow up of all phases, will be realised within 18 months.

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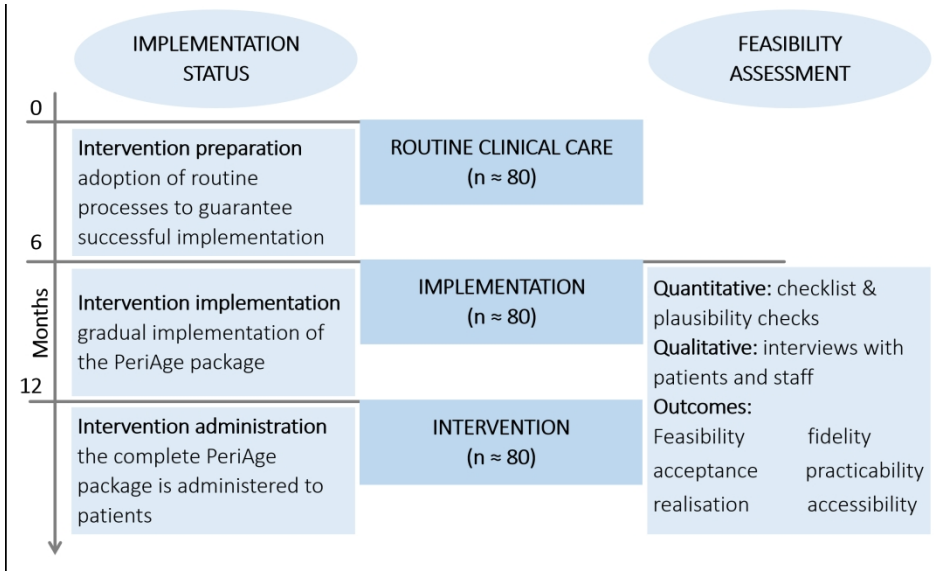

Figure 3. Incorporation of the implementation and feasibility assessment within the study outline. From the implementation phase onwards up to the completion of the intervention phase, the quantitative and qualitative feasibility analyses will be performed.

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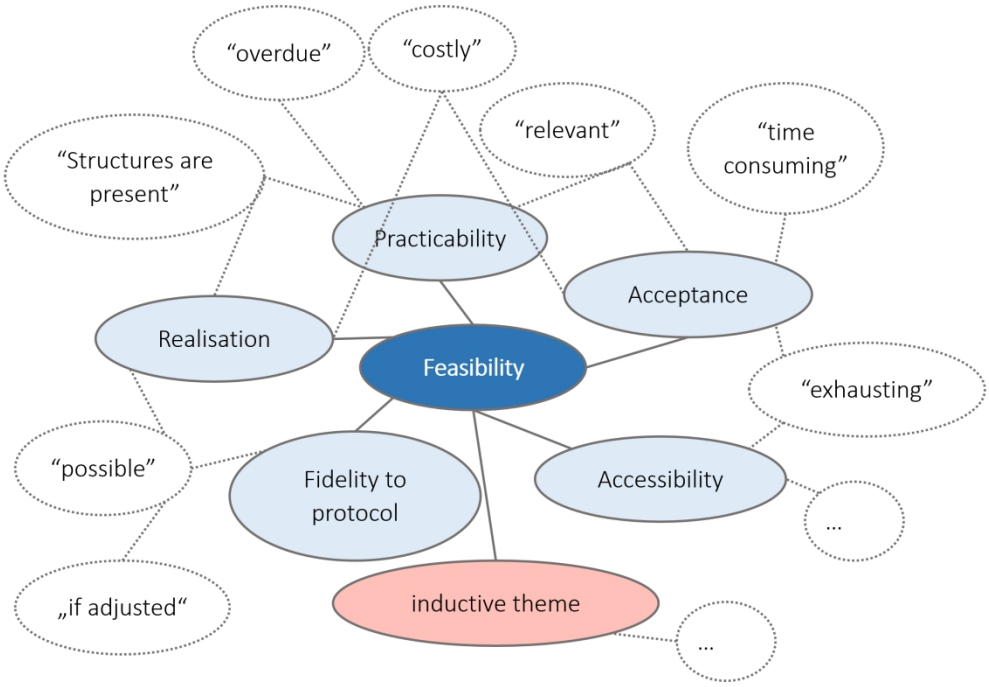

Figure 4. Scheme of theme coding of qualitative feasibility interviews. Potential statements of patients and staff are coded into the different organising aspects of the global feasibility theme.

435x300mm (150 x 150 DPI)

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, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		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	1
Funding	#4	Sources and types of financial, material, and other support	13

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	13
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	13
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)	13
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	3
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 be collected. Reference to where list of study sites can be obtained	5
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	8
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)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#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	6,7,10
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)	6
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including	6

		clinical and statistical assumptions supporting any sample size calculations	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8,11
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	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
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	n/a
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	6,8

		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	
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	9,11
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	9.11
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	9,11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9,11
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)	9,11
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	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these	n/a

		interim results and make the final decision to terminate the trial	
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	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	12
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)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#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	12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
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	12

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: 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	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	12
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	19
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

Reasons for n/a:

Interventions: concomitant care:
as this study is conducted under routine care conditions, all concomitant care is permitted for all patients at all times.

Data monitoring: formal committee:
This is a pilot study, including a process evaluation in which data is monitored as part of the outcome.

Data monitoring: interim analysis:
No interim analysis of the effectiveness subsection of the study is done. Data quality (consistence and completeness) is checked for 6 months into recruitment as part of the process evaluation.

Auditing:

In this pilot study no auditing planned. However in the course of the process evaluation, internal auditing is planned to reveal flaws and deficiencies.

Consent or assent: ancillary studies:

No ancillary studies planned, no biological specimens used.

Ancillary and post trial care:

No ancillary studies planned, no post-trial care and no harm in this study.

Biological specimens:

None used

BMJ Open

Improvement of perioperative care of the elderly patient (PeriAge): protocol of a controlled interventional feasibility study

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Improvement of perioperative care of the elderly patient (PeriAge): protocol of a controlled interventional feasibility study

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ABSTRACT

Introduction Geriatric patients have a pronounced risk to suffer from postoperative complications. While effective risk-specific perioperative measures have been studied in controlled experimental settings, they are rarely found in routine healthcare. This study aims (1) to implement a multicomponent pre- and intraoperative intervention, and investigate its feasibility, and (2) exploratorily assess the effectiveness of the intervention in routine healthcare.

Methods and analysis Feasibility and exploratory effectiveness of the intervention will be investigated in a monocentric, prospective, non-randomised, controlled trial. The intervention includes systematic information for patients and family about measures to prevent postoperative complications; preoperative screening for frailty, malnutrition, strength and mobility with nutrient supplementation, and physical exercise (prehabilitation) as needed. Further components focus on potentially inadequate medication, patient blood-management and carbohydrate loading prior to surgery, retainment of orientation aids in the operating room, and a geriatric anaesthesia concept. Data will successively be collected from control, implementation, and intervention groups. Patients aged 65+ with impending surgery will be included. A sample size of 240, n=80 per group, is planned. Assessments will take place at inclusion and 2, 30, and 180 days after surgery. Mixed-methods analyses will be performed. Exploratory effectiveness will be assessed using mixed segmented regressions. The primary endpoint is functional status. Secondary endpoints include cognitive performance, health-related quality of life, length of inpatient stay and occurrence of postoperative complications. Feasibility will be assessed through semi-structured interviews with staff and patients and quantitative analyses of the data quality, focussing on practicability, acceptance, adoption, and fidelity to protocol.

Ethics and dissemination The study will be carried out in accordance with the Helsinki Declaration and to principles of good scientific practice. The Ethics Committee of the Medical Association Hamburg, Germany approved the protocol (study ID: PV5596). Results will be disseminated in scientific journals and healthcare conferences.

Trial registration ClinicalTrials.gov Identifier: NCT03325413.

Keywords feasibility, perioperative care, elderly, geriatric anaesthesia, anaesthesiology, post-operative complications, complex interventions, instrumental activities of daily life, quality of life, patient-reported outcomes, process evaluation.

Strengths and limitations of this study

+	Feasibility AND exploratory effectiveness evaluation of a multicomponent pre- and intraoperative intervention under real-life circumstances for a variety of surgeries and with few inclusion restrictions.
+	High patient relevance due to the use of a wide range of patient-reported outcome measures and long term follow-up
-	Capturing multidisciplinary experience from anaesthetists, medical assistants, nurses, and patients.
-	Difficulties to implement and control for all intervention components adequately due to real-life circumstances.
	Risk of selection and attrition bias due to the non-randomized design and selective dropout.

INTRODUCTION

In Germany, every second inpatient surgical procedure is performed on patients aged 65 years and above.[1] This cohort has an elevated risk to suffer from a range of postoperative complications (POCs).[2-6] These include postoperative delirium (POD), pulmonary infection, cardiovascular events and an overall higher rate of postoperative morbidity, consequentially extended hospitalisations, and mortality, but also long-term general decline of health, cognition, functional status, and quality of life after surgery.[7-11] Further, immediate POCs can result in and amplify long-term decline of health and long-term loss of functional independence and quality of life. The most common patient-related risk factors are a reduced functional status, (i.a. sensory and cognitive impairment, poor physical fitness and mobility, malnutrition, polypharmacy, and multi-morbidity).[12-15] Treatment-associated risk factors include excessive fasting prior to surgery, dehydration, disorientation, disturbed sleep-wake-cycle, potential-inadequate medication, anxiety, mental overload and -stress, pain, hypothermia, loss of sensory orientation during in-patient stay,[16] and high invasiveness of the anaesthetic procedures and surgery.

In order to reduce POCs and generally improve clinical outcomes in elderly patients, it is important to detect patient-related risk factors prior to surgery and implement appropriate prophylactic measures. Accordingly, risk-specific prehabilitative interventions need to find their way into routine healthcare[12]. Evidence is consistent that preoperative prehabilitative measures can reduce the postoperative risk suffering POCs for elderly patients and hence improve long-term functional status. Protective measures include countering malnutrition,[17,18] poor physical fitness,[19,20] and enhancing breathing exercise techniques,[21] as well as reducing potentially inappropriate or multi-medication.[22,23] Handling of preoperative fasting is another problematic aspect of perioperative care. While guidelines support that 6 hours of preoperative fasting are sufficient in most cases, this is hardly met in clinical practice.[24,25] Recent studies, however, point out the protective effect of preoperative carbohydrate intake on the postoperative outcome, especially in vulnerable patients.[26] Further risk factors for less favourable postoperative outcomes are anxiety and psychological and mental stress. While the necessity of an inpatient surgery alone provokes a stress reaction, so does the entire medical procedure, from preanaesthetic evaluation to inpatient discharge. Last, but not least caused by the unfamiliar environment and the uncertainty of the outcome. This holds particularly true for potentially vulnerable patient groups, as is the geriatric cohort. Stress is well established to negatively impact somatic and mental health outcomes.[27] However, loss of orientation and high levels of stress can be reduced by marginal changes in routine preoperative procedures. Patients can be re-oriented by retaining glasses and hearing aids up to the anaesthetic induction, and by reducing mental stress and overload. This can be done by ensuring that the patient understands the procedures for surgery and therapy and by encouraging the presence and involvement of relatives,[28] which in turn may lead to a higher preservation of preoperative self-reliance and health-related quality of life.[29]

Further, the risk of different intraoperative procedures should be taken into consideration. The risk of suffering POCs is increased in patients, who have blood deficiency states and undergo sanguineous surgery, this risk can be reduced by individualised iron substitution.[30-33] It is recommended to monitor the depth of anaesthesia using e.g. bispectral index (BIS) analysis, as deep anaesthesia is associated with a higher incidence of postoperative delirium.[34] Postoperative pain is a predisposing factor for POCs.[35] To enable sufficient postoperative, opioid-saving analgesia, the use of catheter-assisted regional anaesthesia is preferable for elderly patients.[32,36]

While these risk factors are well studied and several intervention components have been shown to reduce complication rates in controlled research settings,[37-39] many effective intervention components are not used in routine care,[40,41] as both an extensive preoperative risk assessment and the administration of pre- and intraoperative measures are time-consuming and costly.

To improve the geriatric patient's postoperative safety and health, the preanaesthetic evaluation needs to be updated to the current state of research of risk- and preventive factors. Feasibility and benefit of an extended preanaesthetic evaluation and the ensuing administration of corresponding prophylactic interventions need to be demonstrated, in that it is possible to improve the pre- and intraoperative care of geriatric patients with feasible effort, leading to an overall reduction in long-term physical and cognitive complications as well as a reduced hospitalisation period.

Objectives In this study, a demand- and risk-based intervention (PeriAge-intervention) is developed and implemented into routine healthcare.

Objective (1) is to assess and provide exploratory evidence of the effectiveness of the PeriAge-intervention, improving the postoperative outcome of a sample of elderly patients at a university hospital in Germany. The primary outcome is the change in the autonomous functioning after surgery, measured via the Instrumental Activities of Daily Living (IADL, Lawton and Brody, 1969).[42] The corresponding primary hypothesis is that individualized care of the patient as part of the PeriAge intervention enhances postoperative autonomy in comparison to the control group. We expect a smaller reduction of the IADL score in the experimental condition after one, and six months. Additionally, we will test the composite effect of the PeriAge intervention on POCs, cognitive performance, length of inpatient stay, and several patient-relevant outcomes elaborated below.

Objective (2) of our study is to investigate the feasibility[43] of the PeriAge intervention, specifically its implementation and realisation in ongoing hospital operations. We intend to show that it is possible to implement a multidimensional intervention into routine care and identify main challenges of implementation. The feasibility of the implementation is categorised after the elements practicability, acceptance, adoption, and fidelity to protocol.

METHODS AND ANALYSIS

Study design The PeriAge intervention will be evaluated in a monocentric, non-randomized, controlled study. The study consists of three successive arms, each six months in lengths (see figure 1), while lengths of arms remain subject to extension as required. Patients will be allocated in a predefined order; the project starts with the usual routine healthcare as control, followed by the implementation phase and concluded by the intervention phase. Simultaneous to the control phase, the individual components of the PeriAge intervention will be elaborated, and their implementation prepared. The implementation phase is used to implement the PeriAge intervention into routine care gradually, leaving space for adoption, tailoring, and modifications as necessary. With the start of the intervention phase onwards, the final PeriAge intervention will be administered and information of its feasibility will be gathered. The 3-year mixed-method project comprises two simultaneous branches, evaluating the feasibility and effectiveness of the PeriAge intervention, respectively. For reasons of clarity and comprehensibility, the exploratory effectiveness evaluation will be discussed first.

[FIGURE 1]

Study population Participants are patients aged above 64 with impending elective surgery in a university hospital of a German metropolitan region. In order to test the PeriAge intervention with high external validity, patients receiving all types of surgeries except for neurocerebral- and ophthalmologic surgeries will be included. While cognitive performance and functional status cannot be independently attributable to the interventions after neurocerebral surgeries, ophthalmologic surgeries take place at an external site within the university medical centre and execution of intraoperative interventions cannot be guaranteed. Exclusion criteria are emergency surgery, surgery within five days of study inclusion (premedication visit), and surgery with planned postoperative intensive care unit admission or planned postoperative hospitalisation for fewer than 24 hours. Patients that undergo the enhanced recovery after surgery ERAS® programme[44] are excluded. Further, patients will be excluded who are analphabetic, who do not have sufficient command of the German language and patients who suffer from psychosis, illicit drug use, chronic use of benzodiazepines, and patients who suffer from an incorrigible auditory or visual disability.

Effectiveness assessment of the PeriAge intervention and its influences

Procedures and instruments

Within each arm, the study follows a pre-post design. Patient assessments take place once before intervention initiation and at three time points after intervention completion as shown in figure 1. All patients will undergo an extensive preanaesthetic evaluation (T0). In addition to the routine check-up, the assessment entails brief neuropsychological testing, to evaluate the patient's cognitive state,

strength and mobility testing and patient-reported outcome measures (PROMs) about somatic and mental health, current living situation, and quality of life (see table 1). Additionally, the responsible anaesthetist will record malnutrition, demographics, and the need for sensory aids. In the implementation and intervention group the PeriAge intervention will be introduced. However, the implementation group is merely recruited to gradually introduce and adjust the intervention if necessary, to guarantee a fully working and unbiased intervention during the assessment period of the intervention group.

Table 1. Multidimensional perioperative assessment; instruments, type and time point of enquiry and direction of hypothesised effect.

Domain	Instrument	Operationalisation	Time point				exp. direction of effect**
			T0	T1	T2	T3	
Social, physical and autonomous functioning	IADL[42]*	functional status	x		x	x	↑
	Social situation by Nikolaus[45]	social status	x				N/A
	1 minute sit to stand test[46,47]	mobility	x		x	x	↑
	Timed up & go test[48]	physical strength, stamina	x		x	x	↑
	Vigorometer (hand force)[49]	physical strength	x	x	x	x	↑
	LUCAS-FI[50]	frailty proxy	x		x	x	↓
	MNA-SF[51]	malnourishment	x				N/A
orientation & cognition	CAM-ICU[52]	delirium		x			↓
	DemTect[53]	cognitive functioning	x	x	x	x	↑
	TAP alertness subtest[54]		x	x	x	x	↑
	TMT[55]		x	x	x	x	↑
	Subjective cognitive rating	sense of cognitive functioning	x	x	x	x	↑
quality of life & mental health	SF-12[56,57]	health-related quality of life	x		x	x	↑
	GDS[58]	depressive symptoms	x		x	x	↓
	GAD-2[59]	anxiety symptoms	x		x	x	↓
somatic POCs	POSPOM[60]	Postoperative mortality risk scoring	x				N/A

	Patient blood management†	Deficiency states (Hb, Transferritin, Ferritin)	x				N/A
	EPR†	somatic complications (incl. mortality)		x	x	x	↓
	EPR	length of hospitalisation		x			↓
	history assessment	polypharmacy	x				N/A
	IADL*	functional status	x		x	x	↑

POC: post-operative complications. **IADL**: Instrumental Activities of Daily Living. **LUCAS-I**: Longitudinal Urban Cohort Age Study - Instrument (Dapp, Anders, von Renteln-Kruseet al., 2012). **MNA-SF**: Mini Nutritional Assessment- Short From(©Nestlé Nutrition Institute, 1993). **CAM-ICU**: Confusion Assessment Method for Intensive Care Units (Ely, Margolin, Franciset al., 2001). **DemTect**: Dementia Detection (Kalbe, Kessler, Calabreseet al., 2004). **TAP**: Test battery for attentional performance (Zimmermann and Fimm, 1993). **TMT**: Trail Making Test (Reitan and Wolfson, 1992). **SF-12**: Short Form (12) health survey (Bullinger and Kirchberger, 1998). **GDS**: Geriatric Depression Scale (Yesavage, Brink, Roseet al., 1982). **GAD-2**: Generalized Anxiety Disorder 2 (Spitzer, Kroenke, Williamset al., 2006). **POSPOM**: Preoperative Score to Predict Postoperative Mortality (Le Manach, Collins, Rodsethet al., 2016). **EPR**: electronic patient record; *primary effectiveness outcome, all instruments that are administered at T3 and the CAM-ICU will be interpreted as secondary outcomes; † does not fit the description of an instrument, but is listed here for completeness; **the expected effect refers to the comparison between control and intervention group. An up-pointing arrow connotes a reduced respective decline in the intervention group, it does not stand for more favourable values after surgery per se.

The first postoperative enquiry takes place (T1) within the first few days after surgery. At that point, delirium,[53] cognitive functioning,[54-56] physical strength,[46,49] and mobility[47] are assessed and information about somatic complications is extracted from the hospital's electronic patient record (EPR). POD is screened for using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) including modified Richmond Agitation and Sedation Scale (m-RASS) in the first five days following surgery according to guideline recommendations.[61] T2 and T3 take place one and six months after surgery respectively.

Short-term outcomes are duration of inpatient stay, and the occurrence of postoperative complications, including POD and mortality. PROMs and a brief neurocognitive assessment, evaluating patient's postoperative cognitive abilities will be used as parameters to assessing long-term effects of the intervention, one and six months after surgery. PROMs are used to assess functional status, a proxy for frailty, health-related quality of life, and mental morbidity; the neurocognitive assessment focusses

on alertness, cognitive flexibility, and working memory. See *table 1* for instruments, operationalisation, time point of assessment and expected direction of effects.

The proposed intervention components affect either the pre- or the intraoperative phase. While all intervention components shall counteract POC and decline of autonomy one and six months after surgery, the specific measures focus on different aspects of postoperative health. Special attention is given to everyday functioning; including nutritional and fitness status, orientation, and somatic complications.

Malnourished patients will be provided with high-protein drinks for a maximum of 14 days up to the eve of their surgery day. Additionally, patients are offered a carbohydrate drink on the eve and two hours prior to surgery,[62] but also to reduce preoperative anxiety and discomfort.[62,63] Patients with frailty and poor physical fitness are prompted to undergo preoperative progressive strength and fitness training, instructed via a short personal introduction and information brochures and logged by a self-report diary. All patients are advised to perform breathing exercises, as taught by an information brochure.

Interventions

Intervention components to reduce mental overload and prevent disorientation comprise the inclusion of relatives, extensive information giving about planned procedures, and the preservation of sensory orientation. The systematic inclusion of relatives or significant others in all procedures from the beginning of the inpatient stay onwards shall counteract potential disorientation within the unfamiliar, and potentially highly stressful setting. A detailed and comprehensible pre-operation counselling including information about the inpatient stay and the scheduled POC prevention measures shall serve as an additional orientation aid. Patients will be encouraged to bring personal items at admission, such as pillows, photographs, and music. This shall support recognition and diminish the risk of suffering POD. Furthermore, patients with need for vision aids, acoustic instruments, and dental prostheses are encouraged to retain these aids up to the anaesthetic induction to foster sensory orientation.

Measures to prevent somatic complications consist of screening and potential adjustment of potentially inadequate or multi-medication in accordance with national and international recommendations[22,23] and general refrainment from administering benzodiazepines. Patients with anaemia will be screened for iron deficiency. If an iron deficiency anaemia is diagnosed and the risk for intraoperative bleeding is estimated to be above 10%, patients will be supplemented with intravenous iron prior to surgery in accordance of the principles of Patient Blood Management.

The proposed intraoperative measures shall prevent somatic complications and mental disorientation. The geriatric anaesthesia concept includes employing regional anaesthesia alone or in combination with general anaesthesia whenever possible to ensure an opioid-saving postoperative analgesia regime. When general anaesthesia is performed, BIS is used for neuromonitoring purposes. Further, certain medications will be avoided intraoperatively, in particular, benzodiazepines, atropine, anticholinergics, and central alpha-agonists. If muscle-relaxants are needed, short-acting substances are preferred as well as postoperative catheter-assisted analgesia. Thermal blankets from anaesthesia induction to post anaesthesia care will be given to the patient in order to avoid hypothermia.

During the implementation and intervention phases, training events by study staff and external experts will be performed at every affected hospital ward and in anaesthesia meetings. These meetings inform about relevant topics of in-patient care such as the preoperative administration of carbohydrate drinks, measures of POD prevention, patient information and adequate postoperative analgesia in the elderly. Anaesthetists are instructed to follow the comprehensive administration of BIS during surgery.

Recruitment/sample size

In this trial the sample size is motivated by having a reasonable amount of patients undergoing the intervention in order to descriptively and qualitatively describe if the intervention is feasible for being executed in the routine health care. Nevertheless with this sample size we will reach sufficient power for explanatorily identifying rare foreseen and unforeseen incidents, as suggested for feasibility trials.[64,65] The emergence of POCs depends on underlying conditions and type of surgery conducted. In the elected cohort, the likelihood of an occurrence of POCs is considerably above 10%,[66,67] so is the risk of losing the level of preoperative functioning and autonomy. A sample size of 30 is minimally required for the identification of an event with an average occurrence of 10% with a confidence of 95%.[64] Because of an expected dropout greater than 30%, as is common in studies that are performed under routine conditions, together with the plan to analyse multiple outcomes, we aim to recruit 80 patients in each of the three study arms, resulting in approximately 240 patients in total. The effect size of our intervention in our sample is not known as in its present combination it has not yet been tested. However, sufficiently powered effectiveness studies investigating similar populations to ours, aspects of our intervention, and/or on parts of the here assessed complications, came up with similar sample sizes.[68,69]

Data analysis

For the exploratory effectiveness of the intervention, a comparison between the control and the intervention group will be conducted. We plan to use the intention to treat (ITT) method to conduct

the primary analyses. Missing values will be accounted for by using mixed modelling techniques. The data will be analysed using descriptive and inferential statistics. The effects of the intervention will be estimated by using segmented regressions.[70-72] For the effectiveness analyses, generalised two-level regression models (linear, logistic or Cox depending on the outcome) will be used. This enables a nuanced estimation of time- and intervention effects, taking into account time trends within- and between the groups. The first level connotes the progression of the individual patients and will be estimated in intercept and slope. The second level connotes the difference between persons, taking into account time and group-effects. Should the assumptions for segmented regressions be violated, the models will be adjusted accordingly. Propensity score methods will be used in case of strong violation.[73] Results with $p<.05$ will be considered as statistically significant. As this study is of explorative nature, no adjustments will take place for multiple testing. However, the elevated risk of an occurrence of type-I errors will be regarded when interpreting the results.

Feasibility assessment of the implementation

Procedures and instruments

A process evaluation is conducted to explore the feasibility of the PeriAge intervention. The critical elements for capturing the degree of feasibility in this study are acceptance of those affected, in particular patients and clinical staff, as well as the, practicability, realisation and adoption, accessibility of the intervention, and fidelity to protocol, chosen by means of the current standards of feasibility studies (see table 2).[74-76]

Table 2. Quantitative and qualitative feasibility assessment; type and description of analysis.

Domain	Operationalisation	Quantitative analysis	Qualitative analysis***	
		Brief description	Staff	Patient
Acceptance	Satisfaction with the intervention and its implementation	--	x	x
Practicability	Relevance of the intervention and compatibility with the specific setting	(Effectiveness outcomes, see above)	x	x
Realisation and adoption	Realisation: intend and action to employ the intervention	- Data quality analysis on congruency, completeness, plausibility, and sources of potential errors. → reported and adapted if necessary	x	

	Adoption: adjusted execution of the intervention to fit the setting and recording of these adjustments	- descriptive statistics of self-report diary and intervention checklist	
Accessibility	Penetration of intervention and access for all designated and eligible recipients	Evaluation of reasons for non-participation, recruitment progression and attrition rate Analysis of demographics and morbidity of dropouts	x
Fidelity to protocol	Quality and of intervention delivery and adherence to implementation protocol	Evaluation of implementation processes and interim adaptations by intervention checklist records	x

***Thematic analysis evaluation of semi-structured interviews

Using a mixed method approach, the feasibility evaluation is segmented into a quantitative and a qualitative analysis. The quantitative analysis consists of continuous documentation of the realisation of the intervention from the implementation phase onwards (see figure 2).

[FIGURE 2]

An intervention checklist is filled in for every patient. This checklist is tailored on risk factors and interventions of the study and enquires about the proper execution of individual interventions e.g. the reduction of inappropriate polypharmacy, the retainment of orientation aids and the usage of the BIS during surgery. With this collection of process data deviations from the protocol can be prevented, or alternatively, detected. Additional plausibility analyses of the outcome data are performed.

For the qualitative feasibility analyses, information on the experience of the clinical and study staff and patients regarding the individual intervention components are collected and evaluated. Firstly, meeting logs of the project will be described. Secondly, semi-structured interviews will be conducted examining experience and opinion of the interviewee about adequacy and purpose of the intervention, as well as impediments and facilitators of the implementation process. The interviews will contain mainly open-ended questions. Interviewing patients and professionals of different contexts shall capture different perspectives on the implementation and increase the validity of the results. While the patient interviews will be held within the intervention phase after completing the T3 enquiry, the staff interviews will be conducted twice; once during the implementation phase and once after the termination of the intervention phase. The first staff interview serves not only as an inspection of

feasibility, but also allows that necessary adjustments might be exposed and realised. The second interview repeats and finalises the inspection of feasibility.

Recruitment/sample size

Additional to the recruitment of 240 patients for the effectiveness analysis, it is planned to interview 5 to 10 study staff members medical assistants and clinicians, who are affected by the implementation. Additionally, seven randomly chosen patients of the intervention phase will be interviewed. These interviews take place after T3. The chosen sample size is based on experience and literature on saturation of information gain.[77]

Data analysis

To perform the process evaluation, two structured analyses of the process- and outcome data will be performed on congruency and completeness in order to detect potential discrepancies between conception and realisations. The first analysis is conducted before initiation of the implementation phase and the second is conducted after the data collection is completed. The results of the evaluations as well as the results of the intervention checklist (see above), will be examined via descriptive statistics. The interviews will be recorded, transcribed and analysed by using a realist thematic analysis approach,[78] specifically a framework content analysis.[79] The thematic analysis approach is a method by which qualitative data is coded into themes (see figure 3). We will use a mainly deductive approach, as our feasibility outcomes are already pre-defined (see table 2). Coding schemes are developed beforehand and discussed regularly. Nevertheless, we are open to the possibility of inductive theme generation, if data suggests. The results will be reported using consolidated criteria for reporting qualitative research (COREQ).[80]

[FIGURE 3]

Patient and public involvement Patients and public were and will not be directly involved in the research study design. However, within the qualitative analysis, we will assess the patient's opinion of the PeriAge intervention, and about burden and time required to take part in this study. One research question is dedicated to obtain and integrate the patient's opinion into the results and eventually into the decision whether to continue and incorporate the programme in routine care. It is not planned to involve patients in the dissemination of the results. If the intervention shows to be feasible and brings added value into the healthcare of geriatric patients, it will be maintained and expanded to all wards and all surgical geriatric patients in the university medical centre Hamburg-Eppendorf.

Software Microsoft Access will be used for data collection, storage, and preparation. For most quantitative data analyses, it is anticipated to use the software R[81] and IBM SPSS Statistics[82]. Lastly, the software MAXQDA[83] will be used for qualitative data analyses.

ETHICS AND DISSEMINATION

Ethical and safety considerations The study will be carried out according to the Helsinki Declaration of the World Medical Association. The principles of good scientific practice will be followed. Study participation is voluntary and may be withdrawn at any moment. Written informed consent will be obtained prior to participation. Patients will be fully educated about the aims and procedure of the study, data collection and the use of collected data. The rejection of participation has no negative consequences for patients and their care. No foreseeable risk at any moment results from the participation in this study. No compassionate use will be carried out. All intervention components are non-invasive expect for the preoperative iron infusion if required according to the Patient Blood Management protocol. However, this is no experimental therapy method but an established and evidence-based measure, which is executed according to existing guidelines and approved by the local ethical review committee. Preserving principles of data sensitivity, data protection, and confidentiality requirements will be met. Significant deviations from the protocol, concerning recruitment, inclusion criteria, intervention, or statistical data analysis will be justified and discussed. Modifications and amendments will be listed in the appendices of the main publication. SPIRIT reporting guidelines have been used to write protocol.[84]

Dissemination plan The results of the project will be published in scientific journals. In order to assure high accessibility, we aim to publish our work in open access journals, conditions permitting. Furthermore, the results will be presented at relevant national and international conferences. Additionally, a data basis shall be created that will help to inform clinical practice guidelines that enable and improve perioperative care and surgical outcomes of geriatric patients, respectively.

Data deposition The collected data will be deposed on a protected server of the University Medical Centre Hamburg-Eppendorf, with strongly regulated access even for study personnel. Due to substantial obstacles to de-identification (relatively small sample, routine care, a large amount of qualitative data, etc.), individual participant data will not be shared publicly. Researchers who submit a methodologically sound proposal to the principal investigator that is approved by the responsible review committee will be allowed to use data.

AUTHORS CONTRIBUTORS

CO, MH, RK, and LK conceptualised the study, wrote the grant proposal, and obtained funding. LL, CO, AM, and LK designed the details of the study, with substantial contributions from MH and RK. RK is the responsible primary investigator of the project. LL and CO prepared the first draft of the manuscript. LP substantially contributed to implementing the individual interventions and the recruitment of patients. AEG and CZ, heads of the UKE Anaesthesiology department, supported and enabled the realisation of the study with their overall supervision. All authors contributed to critically revising the manuscript for important intellectual content, gave final approval of the version to be published, and agree to be accountable for the work as guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests None declared.

Patient consent Not required.

Ethics approval Ethics Committee of the Medical Association Hamburg, Germany (study ID: PV5596).

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SUPPLEMENTARY FIGURE LEGENDS

Figure 1 Sequential study design. Allocation randomisation is not feasible, due to the risk of contamination or cross over between groups. During the control and implementation phase, the intervention components will be developed, the implementation planned and gradually introduced. In the intervention phase, the exhaustive intervention will be applied. The enquiry period, entailing recruitment and follow up of all phases, will be realised within 18 months.

Figure 2 Incorporation of the implementation and feasibility assessment within the study outline. From the implementation phase onwards up to the completion of the intervention phase, the quantitative and qualitative feasibility analyses will be performed.

Figure 3 Scheme of theme coding of qualitative feasibility interviews. Potential statements of patients and staff are coded into the different organising aspects of the global feasibility theme.

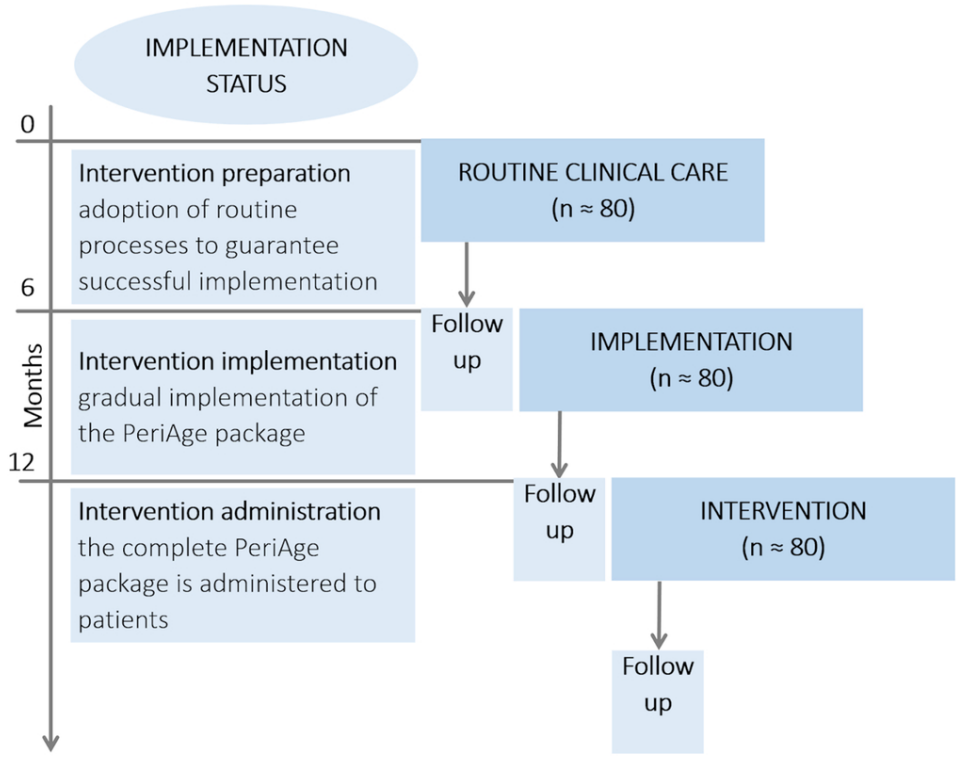

Figure 1 Sequential study design. Allocation randomisation is not feasible, due to the risk of contamination or cross over between groups. During the control and implementation phase, the intervention components will be developed, the implementation planned and gradually introduced. In the intervention phase, the exhaustive intervention will be applied. The enquiry period, entailing recruitment and follow up of all phases, will be realised within 18 months.

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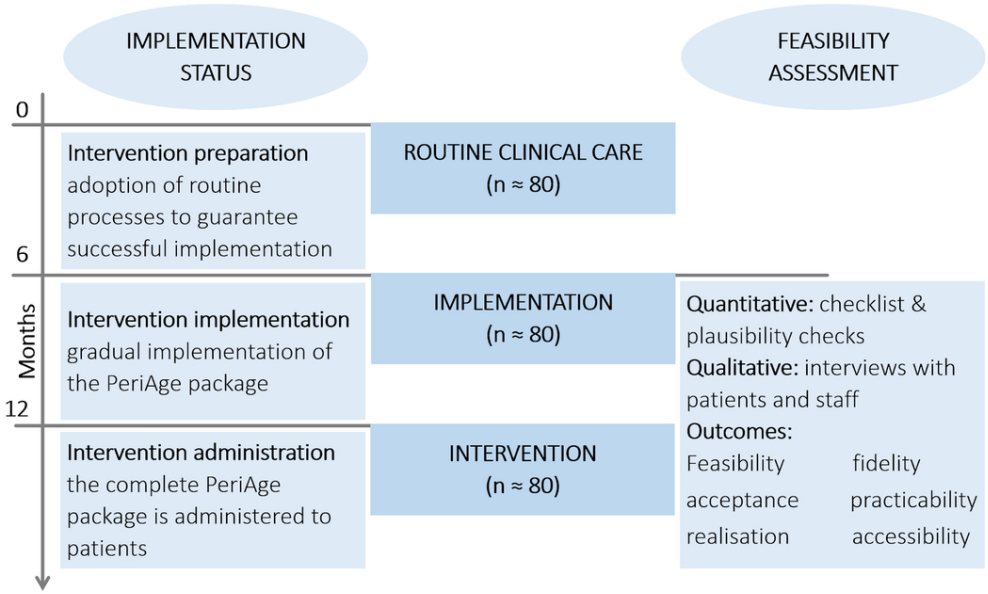

Figure 2 Incorporation of the implementation and feasibility assessment within the study outline. From the implementation phase onwards up to the completion of the intervention phase, the quantitative and qualitative feasibility analyses will be performed.

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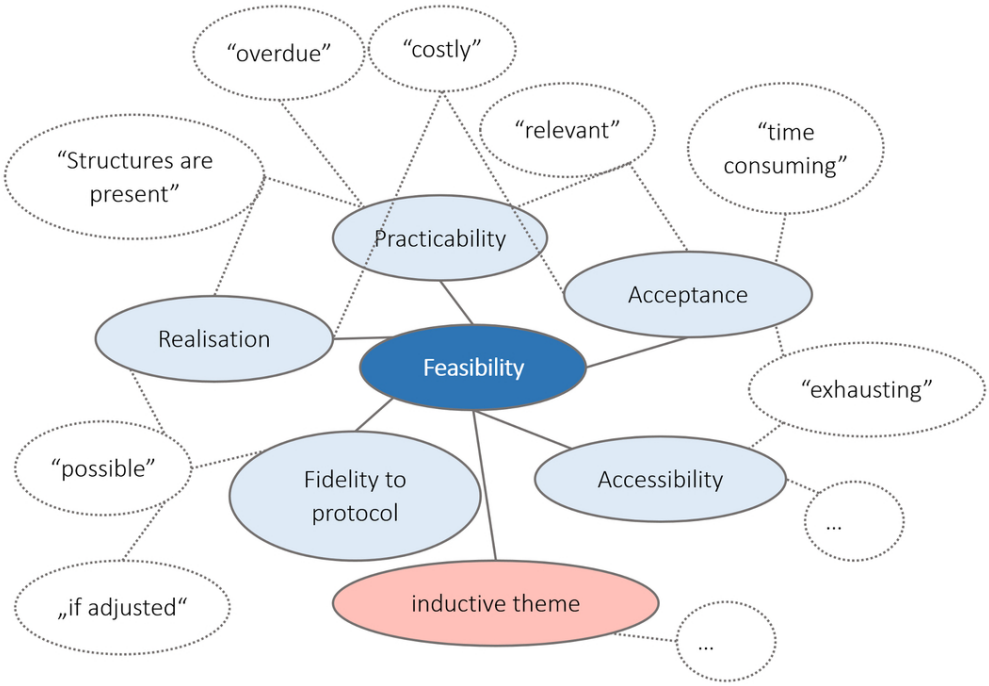

Figure 3 Scheme of theme coding of qualitative feasibility interviews. Potential statements of patients and staff are coded into the different organising aspects of the global feasibility theme.

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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, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		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	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 13

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	13
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	13
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)	13
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	3-4
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 be collected. Reference to where list of study sites can be obtained	5
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	8

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)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#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	6,7,10
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)	6
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	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9,11
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	5

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
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	n/a
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. Reference to where data collection forms can be found, if not in the protocol	7-8,10-11
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	9,11
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	9,11
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	9,11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9,11
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)	9,11
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	n/a

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	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	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	12
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)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#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	12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
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	12-13
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: 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	12

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	13
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
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

Reasons for n/a:

Interventions: concomitant care:

as this study is conducted under routine care conditions, all concomitant care is permitted for all patients at all times.

Data monitoring: formal committee:

This is a pilot study, including a process evaluation in which data is monitored as part of the outcome.

Data monitoring: interim analysis:

No interim analysis of the effectiveness subsection of the study is done. Data quality (consistence and completeness) is checked for 6 months into recruitment as part of the process evaluation.

Auditing:

In this pilot study no auditing planned. However in the course of the process evaluation, internal auditing is planned to reveal flaws and deficiencies.

Consent or assent: ancillary studies:

No ancillary studies planned, no biological specimens used.

Ancillary and post trial care:

No ancillary studies planned, no post-trial care and no harm in this study.

Biological specimens:

None used