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Study Protocol with Statistical Analysis Plan (SAP)

Comparison of two skin protection regimes for the Prevention of Incontinence-associated Dermatitis in geriatric care: An exploratory trial (PID)

Study Code: PID

NCT Number: NCT05403762

Study Protocol V1.1, 15 June 2022; SAP V4, 17 April 2025

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FUNDING

Bundesministerium für Bildung und Forschung (BMBF), FKZ 01KG2020

I. SUMMARY

Title of the clinical study	Comparison of two skin protection regimes for the Prevention of Incontinence-associated Dermatitis in geriatric care: an exploratory trial (PID)
Funding	Bundesministerium für Bildung und Forschung (BMBF), FKZ 01KG2020
Investigators	Prof. Dr. rer. cur. Jan Kottner Priv.-Doz. Dr. rer. cur. Nils Lahmann
Study period	July 2022 to January 2024
Study design	Randomized controlled, parallel group, three-arm, assessor-blinded exploratory trial
Number of subjects	• To be assessed for eligibility (n = 500 subjects) • To be allocated to trial (n = 210 subjects; n = 70 per study arm) • To be analyzed (n = 180 subjects; n = 60 subjects per study arm)
Objectives	The primary research objective is to compare the incidence of incontinence-associated dermatitis (IAD) in two intervention groups and one control group and to estimate effect sizes for a possible subsequent confirmatory randomized controlled trial (RCT). Additional objectives are to test the feasibility of conducting a confirmatory RCT to prevent IAD and to evaluate the feasibility of measuring the Core Outcome Domains for IAD trials.
Outcomes	• IAD incidence • Erythema • Erosion • Maceration • IAD-related pain • IAD-related itch • Satisfaction with treatment • Willingness to participate • Retention • Adherence to prescribed intervention • *Adverse Events (AEs)* and *Serious Adverse Events* (SAEs) according to the definition of the EU regulation 2017/745 Medical Device Regulation (MDR) Article 2 (57) and (58) • *Incidents* and *Serious Incidents* according to the definition of the EU regulation 2017/745 MDR Article 2 (64) and (65)

Eligibility criteria	**Institutional Level** Inclusion criteria: • Nursing home, geriatric hospital or hospital with geriatric ward(s) in the federal state of Berlin • Expression of a clear commitment to apply the study related procedures • Willingness to regularly allow study related trainings (on site at the nursing home/ hospital, conducted by study personnel) and to allow and ensure the participation by a sufficient number of employees • Agreement that study-related documents, such as diaries, will be completed daily by involved caregivers to ensure compliance and that study personnel may review these documents on a regular interval • Commitment to adhere to the trial procedures Exclusion criteria: • Any circumstance that makes it unfeasible to conduct the study in the nursing home/ hospital in accordance to the study protocol **Participant Level** Inclusion criteria: • Geriatric patients or residents (≥ 65 years) staying/living in one of the participating institutions • being incontinent of urine and stool • Expected minimum length of stay of 14 days • Intact skin with no clinical signs of IAD **OR** intact skin with early clinical signs of IAD but without clinical signs of infection (GLOBIAD category 1 A) • Written informed consent Exclusion criteria: • Residents/patients at the end of life • Residents/Patients with skin loss due to IAD (GLOBIAD category 2 A) and/or signs of clinical infection in the IAD area (GLOBIAD category 1 B or2 B) • Any other skin condition or wounds (at investigational areas of the skin) requiring additional treatment (including but not limited to pressure ulcers, intertrigo, infection) • Known hypersensitivity or allergy to silicones and/or topical leave-on products

	• Topical treatments in the IAD area.
Intervention(s)	• **Experimental intervention I:** Standardized mild skin cleansing regimen and daily topical application of a film-forming skin protectant at the exposed skin areas. • **Experimental intervention II:** Standardized mild skin cleansing regimen and daily topical application of a hydrophobic skin protectant at the exposed skin areas. • **Control intervention:** Standardized mild skin cleansing regimen without application of an additional skin protectant.
Duration of treatment	• Duration of intervention per patient: 14 days • Follow-up per patient: 14 days
Statistical methods	Efficacy: The endpoints will be compared descriptively between the three groups. No confirmatory statistical tests will be conducted. Description of the primary efficacy analysis and population: The intention-to-treat (ITT) principle will be applied, including all subjects that were allocated to a study group. Safety: AEs, SAEs, incidents and serious incidents will be listed per patient and for the total trial.

II. TABLE OF CONTENTS

III. TABLES AND FIGURES

IV. LIST OF ABBREVIATIONS

Abbreviation	
AE	Adverse Event
BlnDSG	Berliner Datenschutzgesetz
BMBF	Bundesministerium für Bildung und Forschung
BMI	Body Mass Index
CRF	Case report form
CTO	Clinical Trial Office at the Charité
DMP	Data management plan
DRKS	Deutsches Register Klinischer Studien (German Clinical Trials Register)
DSGVO	Datenschutzgrundverordnung (General Data Protection Regulation)
EC	Ethics committee
EU	European Union
eCRF	Electronic case report form
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GDS	Global Deterioration Scale
GLOBIAD	Ghent Global IAD Categorization tool
IAD	Incontinence associated dermatitis
ICD	International Classification of Diseases
ICF	Informed consent form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IPD	Individual patient data
ISF	Investigator Site File
IIT	Investigator Initiated Trial
ITT	Intention-to-treat
MDR	Medical Device Regulation
MPDG	Medizinprodukterecht-Durchführungsgesetz
NRF	Neues Rezeptur Formularium
NRS	Numeric Rating Scale
PU	Pressure Ulcer
QoL	Quality of life
RDE	Remote Data Entry
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Source documents
SGB	Sozialgesetzbuch (Codebook of Social Law)
SOP	Standard operating procedure
SPSS	Statistical Package for the social science
SSL	Secure Sockets Layer
WHO	World Health Organization

V. ADMINISTRATIVE INFORMATION

Title

Comparison of two skin protection regimes for the Prevention of Incontinence-associated Dermatitis in geriatric care: An exploratory trial (PID)

Trial registration

This trial is registered at the German Clinical Trials Register https://www.drks.de (DRKS00028954) (Deutsches Register Klinischer Studien; DRKS) and at clinicaltrials.gov (NCT05403762). The local ethics committee of the Charité - Universitätsmedizin Berlin approved the trial on April 07, 2022 (EA4/043/22).

Protocol version

Version 1.0, 25 May, 2022

Funding

This study is conducted by the Institute for Clinical Nursing Science, Charité – Universitätsmedizin Berlin and the Research Group Geriatrics, Charité – Universitätsmedizin Berlin. The trial is supported by the Federal Ministry of Education and Research (BMBF).

Roles and responsibilities

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1. INTRODUCTION

1.1 BACKGROUND AND RATIONALE

Incontinence-associated dermatitis (IAD) is an unwanted skin condition which is common in incontinent individuals. It is an inflammatory skin response due to repeated or prolonged contact with urine and/or stool [1, 2]. It can occur throughout the lifespan, thus it is present in babies and young children ("diaper dermatitis") as well as in the older individuals [1].

The prevalence of incontinence rises with increasing age [3]; therefore, IAD is more common in the aged population. IAD prevalence is 3% to 23% in long-term geriatric care and 15% to 40% in acute care settings [4]. A representative prevalence study in institutional geriatric long-term care facilities showed an IAD prevalence of 35.4% [5, 6]. Thus, around one in three residents was affected by some form of IAD.

Clinically, IAD is manifested by skin redness, vesicles, nodular thickening and maceration of the tissue as well as defects of the skin up to the loss of the upper skin layers. For those affected, this can be a physical as well as psychological burden. In addition to pain, burning, and itching, IAD is associated with an increased risk of secondary infections and the development of pressure ulcers (PUs) [7, 8]. As a result of these changes, affected individuals may also suffer from a reduced quality of life, for example, through a loss of independence, reduction of social activities, or poor sleep due to IAD-related pain or itch [6, 9, 10].

With approximately 80%, the majority of residents in geriatric long-term care facilities, as well as a high proportion of geriatric patients in acute care settings, are affected by one form of incontinence and are therefore at potential risk of developing IAD [11-13]. If adequate preventive measures are taken at an early stage, IAD might be avoided. However, the high prevalence of IAD in these settings indicates that current prevention strategies are not optimal. Due to a lack of knowledge, the current nursing practices in the context of IAD prevention are mainly influenced by individual traditions and personal preferences and are not evidence-based [14]. At the same time, a clear need for support as well as assistance is expressed on the part of nurses and other caregivers in order to be able to perform an efficient and effective IAD prevention [15]. Therefore, it is an important aim to close existing evidence gaps in this area to support nurses and other caregivers with a solid scientific base for IAD prevention. The planned trial aims a direct comparison of the two most important skin protection product categories in the form of an explorative randomized controlled trial (RCT), taking core outcomes for IAD research into account.

1.2 OBJECTIVES

The primary research objective is to compare the incidence of IAD in the intervention and control groups to estimate effect sizes for a possible subsequent confirmatory RCT. Another objective is to evaluate the feasibility of the planned interventional skin care regimen in geriatric populations. This will be the first time, the recently developed set of IAD-specific outcomes (CONSIDER) [16] will be used and evaluated in the context of a clinical trial. This Core Outcome Set (COS) is intended to improve the comparability and pooling of future data from different studies in the field of IAD research to provide a basis for evidence-based health care.

The trial will answer the following research questions:

- What are the effect sizes of the outcomes?
- Is the implementation of a standardized skin protection regime for the prevention of IAD feasible in geriatric hospital wards and nursing homes?
- Does the implementation of a standardized skin protection regime for the prevention of IAD reduce itch and IAD-related pain?
- Is the measurement of Core Outcome Domains for IAD trials feasible?

1.3 TRIAL DESIGN

Randomized controlled, parallel group, three-arm, assessor-blinded exploratory trial

2. METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

2.1 STUDY SETTING

The study will be conducted in geriatric hospitals/geriatric wards of participating hospitals and in institutional long-term care facilities of the federal state of Berlin, Germany.

2.2 ELIGIBILITY CRITERIA

2.2.1 INSTITUTIONAL LEVEL

Inclusion criteria:

(1) Nursing home, geriatric hospital or hospital with geriatric ward(s) in the federal state of Berlin
(2) Expression of a clear commitment to apply the study related procedures
(3) Willingness to regularly allow study related trainings (on site at the nursing home/ hospital, conducted by study personnel) and to allow and ensure the participation by a sufficient number of employees
(4) Agreement that study-related documents, such as diaries, will be completed daily by involved caregivers to ensure compliance and that study personnel may review these documents on a regular interval
(5) Commitment to adhere to the trial procedures

Exclusion criteria:

(1) Any circumstance that makes it unfeasible to conduct the study in the nursing home/ hospital in accordance to the study protocol

2.2.2 RESIDENT/PATIENT LEVEL

Inclusion criteria:

Geriatric patients (≥ 65 years) admitted to geriatric wards of participating hospitals or residents of participating nursing homes can be included if the following criteria are met:

(1) Being incontinent of urine and stool
(2) Expected minimum length of stay of 14 days
(3) Intact skin with no clinical signs of IAD

OR

Intact skin with early clinical signs of IAD (erythema) but without clinical signs of infection (GLOBIAD category 1 A)

(4) Written informed consent (by legal representative, if required)

Exclusion criteria:

(1) Residents/patients at the end of life
(2) Residents/Patients with skin loss due to IAD (GLOBIAD category 2 A)and/or signs of clinical infection in the IAD area (GLOBIAD category 1 B, category 2 B)
(3) Any other skin condition or wounds (at investigational areas of the skin) requiring additional treatment (including but not limited to pressure ulcers, intertrigo, infection)
(4) Known hypersensitivity or allergy to silicones and/or topical leave-on products
(5) Topical treatments in the IAD area.

2.3 INTERVENTIONS

Included participants of all three groups receive a standardized skin cleansing regime consisting of cleansing of the skin with water and the addition of a mild cleansing product. Cleansing is done using disposable washing mitts. To remove possible residual stool from the skin, an additional skin oil can be used. After subsequent gentle drying of the skin, elastic disposable breathable incontinence pants are put on. This is considered as 'standard incontinence care'. In order to ensure the greatest possible standardization and uniformity, the same predefined products and procedures are used for all participants. The required products for the participants will be provided by the investigators and are listed in Table 1.

After baseline visits, included residents/patients will be randomly assigned on Day 0 to one of the following three study arms:

- **Study arm 1 (Experimental intervention I):** Standard incontinence care with additional daily topical application of a film-forming leave-on skin protectant (ESENTA™ Hautschutz Spray) that builds a protective layer on the surface of the skin
- **Study arm 2 (Experimental intervention II):** Standard incontinence care with additional daily topical application of a lipophilic leave-on skin protectant (Hydrophobes Basisgel DAC) that forms a hydrophobic physical barrier on the skin
- **Study arm 3 (Control group):** Standard incontinence care alone, no additional intervention in the control group

The interventions are described in detail according to the template for intervention description and replication (TIDieR) checklist [17] in Table 1. The items 10 and 12 do not apply for study protocols and are therefore not listed in the table [17].

Table 1: Description of interventions according to the template for intervention description and replication (TIDieR) [17].

Item	Experimental intervention I	Experimental intervention II	Control group
1. Brief name	Film-forming leave-on skin protectant for IAD prevention	Hydrophobic leave-on skin protectant for IAD prevention	No skin protectant
2. Rationale	Film-forming topical leave-on products are widely used to protect the skin from irritants including urine and/or stool in incontinent patients [18, 19]. Whether film-forming products are better than hydrophobic ointments/emulsions or no skin protectants is unclear.	Monophasic or biphasic hydrophobic (emulsions) topical leave-on products are widely used to protect the skin from irritants including urine and/or stool in incontinent patients [18]. Whether hydrophobic leave-on products are better than film-forming products or no products is unclear.	Most incontinent patients do not receive any topical skin protectant when the skin is intact. The relative and absolute benefit of applying any skin protectant to intact skin of incontinent geriatric patients in unclear.
3. Materials	- Skin will be cleansed with water and the addition of a **mild cleanser** (preferably non-alkaline skin cleansers with a pH range similar to normal skin and non-ionic surfactants, e.g. Bübchen Creme Pflegebad, Nestlé Nutrition GmbH, Germany) using **disposable wash mitts/cloths** (e.g. Waschhandschuh PLUS, Desomed AG, Germany) - A **skin oil** (perfume-free, dye-free, e.g. Baby Öl, Nestlé Nutrition GmbH, Germany) may be used in addition to remove stool. **- ESENTA™ Skin Barrier** (ConvaTec Inc., UK) will be applied on clean and dry skin exposed to urine and stool. After application, the solvent evaporates leaving a silicone film on the skin surface. - Elastic **disposable breathable incontinence pants** are put on (e.g. Seni active classic, TZMO Deutschland GmbH, Germany).	- Skin will be cleansed with water and the addition of a **mild cleanser** (preferably non-alkaline skin cleansers with a pH range similar to normal skin and non-ionic surfactants, e.g. Bübchen Creme Pflegebad, Nestlé Nutrition GmbH, Germany) using **disposable wash mitts/cloths** (e.g. Waschhandschuh PLUS, Desomed AG, Germany) - A **skin oil** (perfume-free, dye-free, e.g. Baby Öl, Nestlé Nutrition GmbH, Germany) may be used in addition to remove stool. - **Hydrophobes Basisgel DAC** will be applied on clean and dry skin. It contains 95% paraffin oil and creates a hydrophobic layer on the skin surface [20]. - Elastic **disposable breathable incontinence pants** are put on (e.g. Seni active classic, TZMO Deutschland GmbH, Germany).	- Skin will be cleansed with water and the addition of a **mild cleanser** (preferably non-alkaline skin cleansers with a pH range similar to normal skin and non-ionic surfactants, e.g. Bübchen Creme Pflegebad, Nestlé Nutrition GmbH, Germany) using **disposable wash mitts/cloths** (e.g. Waschhandschuh PLUS, Desomed AG, Germany) - A **skin oil** (perfume-free, dye-free, e.g. Baby Öl, Nestlé Nutrition GmbH, Germany) may be used in addition to remove stool. - Elastic **disposable breathable incontinence pants** are put on (e.g. Seni active classic, TZMO Deutschland GmbH, Germany).
4. Procedures	After regular skin cleansing in the morning, the skin protectant is applied to dry skin.	After regular skin cleansing in the morning and evening, the skin protectant is applied to dry skin. In addition, the product is reapplied following the skin cleansing after a stool incontinence episode.	After regular skin cleansing, no additional skin protectant is applied.
	Prior to the beginning of the study, ward nurses are educated in interactive face-to-face meetings. Handouts will be provided and posters summarizing the study procedures are placed on the wards. Regular refresher meetings are held every three months under the supervision of the investigators.		

5. Who provides?	Ward nurses who participated in an educational session about this study and the procedures and thus have study-relevant knowledge.		
6. How	- After removal of the incontinence briefs, the skin is cleansed and dried. - An oil may be used to remove stool and/or residual products. - The skin protectant is applied to dry skin. According to manufacturer instructions, the spray must be hold approximately 10 cm away from the skin surface. A uniform layer of the product is applied using a sweeping motion over the area to be protected. The film must be completely dry before the person is turned onto their back, new incontinence materials are placed or clothing is put on. - New incontinence pants are put on (if needed from the view of the nurses).	- After removal of the incontinence briefs, the skin is cleansed and dried. - An oil may be used to remove stool and/or residual products. - The skin protectant is applied to dry skin. - New incontinence pants are put on (if needed from the view of the nurses).	- After removal of the incontinence briefs, the skin is cleansed and dried. - An oil may be used to remove stool and/or residual products. - New incontinence pants are put on (if needed from the view of the nurses).
7. Where	In the patient rooms, in or outside of the bed.		
8. When and how much	It is widely assumed that polymeric films protect the skin up to 72 hours [21]. According to manufactures instruction, reapplication of ESENTA™ Skin Barrier (ConvaTec Inc., UK) is recommended every 12 to 72 hours. To ensure sufficient skin protection and to standardize application within this trial, the product will be applied once daily in the morning as a uniform film to cover the exposed skin area.	Because traditional lipophilic leave-on products do not adhere to the skin surface that strongly, it may be removed more easily. To ensure sufficient protection the Hydrophobes Basisgel DAC will be applied twice daily (in the morning and evening) as a thin layer on the skin exposed to urine and stool.	Not applicable
9. Tailoring*	The frequency and intensity of skin cleansing and the application of new incontinence material will be based on the number and intensity of incontinence episodes.		
	Not applicable	The skin protectant will be reapplied in addition after every stool removal from the skin.	Not applicable
11. How well*	Ward nurses are initially trained and retrained after 3 months, after 6 month, and as needed at individual additional meetings. During the study, the nurses continuously document the study related procedures performed (cleansing, use of leave-on products, used materials) in a resident/patient-specific diary. The study personnel check these diaries daily for completeness and consistency to ensure and improve compliance and adherence to the protocol.		

*****Item 10 and 12 do not apply for study protocols and are therefore not listed in the table

2.3.1 QUALITATIVE INTERVIEW PART

In total, n = 12 qualitative interviews will be conducted with four patients per study group to explore the patient perspectives and preferences regarding IAD prevention. This number is based on the recommendations for doing qualitative research in feasibility studies for RCTs [22]. To consider possible sex related differences, two male and two female participants will be included per group. To be eligible, patients need to have a MMSE score of 24 or higher. A separate consent is required for participation in the interview. Interviews will be transcribed verbatim and qualitative content analyzes conducted.

2.3.2 CRITERIA FOR DISCONTINUING

Nursing home/hospital level:

(1) If the institution no longer wants to participate,
(2) Any circumstance that makes it impossible or irresponsible to continue study at the respective institution

Resident/patient level:

(1) If a participant or its legal representative withdraws its consent,
(2) Adverse events (AEs) that, in the judgment of study personnel, interfere with further participation in the trial,
(3) Serious adverse events (SEAs),
(4) Incidents that, in the judgment of study personnel, interfere with further trial participation,
(5) Serious incidents,
(6) The occurrence of a medical condition which is incompatible with continued trial participation. These include, for example:
    a. Mycotic or bacterial inflammation, or other skin conditions in the study area that require topical (drug) treatment of the skin area with other products,
    b. The development of a category II, III, IV pressure ulcer, or an unstageable pressure ulcer, or a suspected deep tissue injury (DTI)
(7) If participants are permanently transferred outside the study site
(8) In the intervention groups: missing application of study products for more than 72 hours
(9) More than three missing study visits

An "adverse event" or "serious adverse event" is in accordance with the definitions of Regulation (EU) 2017/745 (MDR) as defined in Article 2(57) and (58). An "incident" or "serious incident" is in accordance with the definitions of Regulation (EU) 2017/745 (MDR) as defined in Article 2(64) and (65).

For the whole trial:

(1) If the ethics committee withdraws the ethics approval
(2) If after 8 months of recruitment less than n = 60 participants have been included
(3) The CTAB unanimously decides after 8 months that study continuation is not suitable to answer the research questions.

2.4 EDUCATION

2.4.1 TRAININGS

Training courses of 60 minutes will be conducted by the research team to educate the nurses and involved care givers in study-relevant procedures. This includes the demonstration of the study related procedures by the research team as well as an exercise for the caregivers on the correct use of the products. The trainings will be conducted before the study starts in the participating institutions. The number of trainings held initially is based on the number of staff to be trained, to ensure that a sufficient number of the involved caregivers have received the training. At regular intervals of about three months, follow-up training sessions are conducted by the study staff in the institutions to check and refresh knowledge about the study and its procedures and to involve new caregivers.

2.4.2 MATERIALS

In addition to the trainings, written/illustrated instructions, explaining the correct use of materials and describing the protocol-compliant conduct of study related procedures, will be provided to give nurses the possibility to review and refresh relevant information at any time. It is planned that these materials will be made available in print as well as digital form. For this purpose, booklets and presentations will be prepared. Furthermore, DIN-A1 posters will be placed in the participating wards to increase the awareness of the study and to provide a quick overview of the related procedures at any time.

In addition, color-coded laminated cards will be placed in the participants' rooms, preferably close to their incontinence materials. The color of the card reflects the assignment to the study

group and contains a minimum of information about the correct conduct of procedures in the respective study group. These cards will serve as a reminder for caregivers and help to avoid confusion regarding group assignment. Measures to prevent accidental unblinding of the outcome assessor are taken (see section 3.3 , page 31).

2.5 STRATEGIES TO IMPROVE COMPLIANCE AND ADHERENCE TO THE STUDY PROTOCOL

Prior to inclusion of an institution, interested institutions are visited by the study coordinators. During this visit, the background and procedures of the study are explained and the importance of adhering to the study protocol and the provision of sufficient nurses and other caregivers is emphasized. If the study coordinators are confident that the institution meets the requirements, has the impression that the study-related procedures can be performed correctly and the institution demonstrates willingness to participate, the institution is eligible for inclusion in the study. Prior to participation, institutions sign a written informed consent form. After inclusion, ongoing communication with nursing homes and hospitals will be maintained throughout the study to prevent premature loss of participating institutions.

During the study visits in the participating institutions, the study personnel will review diaries completed by the caregivers at least every second day. The high frequency of visits will increase the caregivers' attention of the study and provide the opportunity for regular communication between the caregivers and the study staff. The study staff can immediately identify missing data and inconsistencies in the diaries and discuss and resolve them directly with the caregivers. This timely and prompt approach will significantly contribute to data quality and completeness. Likewise, the caregiver has the opportunity to clarify open questions with the study staff promptly at any time.

2.6 CONCOMITANT CARE AND INTERVENTIONS

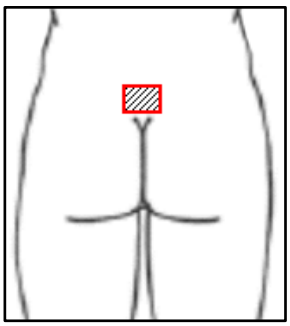
According to the pragmatic nature of this study there are no restrictions regarding concomitant care or treatments as long as they do not interfere with the conduct of the study.

2.7 OUTCOMES AND VARIABLES

Because of the exploratory nature of the trial and according to methodological guidance for exploratory trials, a distinction between primary and secondary endpoints is not made [23]. Because the main aim is to prevent IAD, IAD incidence is likely to be considered as a primary outcome in a possible subsequent confirmatory trial.

Table 2: Outcomes and variables per participant

Outcome Name	Device/Measurement instrument/Scale and metric	Time points	Response Options/Categories/ Range
IAD incidence	• **IAD Classification** according to GLOBIAD [24] and distinction between intact and eroded skin according to *Proceedings of the Global IAD Expert Panel* [10] • Cumulative incidence • **IAD Localization** according to the following definition: ○ **Back:** Sacral region going down to the upper thighs, bordered approximately 5 cm below the gluteal fold ○ **Front:** Navel to upper thigh	Days 0, 2, 4, 6, 8, 10, 12, 14	• **Presence of IAD:** (1) None; (2) Category 1 A; (3) Category 1 B; (4) Category 2 A; (5) Category 2 B • **Localization of IAD:** (1) Back (2) Front
Erythema	• Rating according to the item 'Redness' of the incontinence-associated dermatitis and its severity (IADS) instrument [25] • 3-Item-Scale (ordinal)	Days 0, 2, 4, 6, 8, 10, 12, 14	• **Redness:** (1) None; (2) Pink; (3) Red/Bright red

Outcome Name	Device/Measurement instrument/Scale and metric	Time points	Response Options/Categories/ Range
	• Mexameter MX18 with MDD 4 (Courage + Khazaka Electronic GmbH) [26] (measurements according to SOP „Mexameter® MX 18" Version 1.0, 18.05.2022) (see **Fehler! Verweisquelle konnte nicht gefunden werden.**) • Arbitrary units (AU) from 0 (= no erythema) to 999 (= extreme erythema) • Means of duplicate measurements at the cranial end of the gluteal cleft 	Days 0, 2, 4, 6, 8, 10, 12, 14	• **Erythema level:** 0 - 999 [numeric; AU]
Erosion	• Definition of erosion according to the latest International League of Dermatological Societies glossary of cutaneous lesions [27]: *"Loss of either a portion of or the entire epidermis"*	Days 0, 2, 4, 6, 8, 10, 12, 14	• **Presence of Erosion:** (1) No; (2) Yes
Maceration	• Definition of maceration according to review article [28]: *"(…) maceration (…) is the result of prolonged exposure (of the skin) to moisture and causes the skin to soften and breakdown so that the connective fibres can be teased apart and the skin often exhibits a white appearance."*	Days 0, 2, 4, 6, 8, 10, 12, 14	• **Presence of Maceration:** (0) No; (1) Yes

Outcome Name	Device/Measurement instrument/Scale and metric	Time points	Response Options/Categories/ Range
IAD related pain	• Numeric rating scale (NRS) from 0 (= no pain) to 10 (= worst possible pain) (see **Fehler! Verweisquelle konnte nicht gefunden werden.**) for patients/residents without cognitive impairment (according to Mini-Mental-State-Examination (MMSE) [29] with scores of 24 or higher) • Means	Days 0, 2, 4, 6, 8, 10, 12, 14	• **IAD related pain:** 0 - 10 [numeric]
	• Pain Assessment in Advanced Dementia (PAINAD-G) scale [30, 31] (see **Fehler! Verweisquelle konnte nicht gefunden werden.**) will be used for patients/residents with dementia (according to MMSE [29] scores of < 24; see **Fehler! Verweisquelle konnte nicht gefunden werden.**) • Means	Days 0, 2, 4, 6, 8, 10, 12, 14	• **IAD related pain:** 0 - 10 [numeric]
Patient satisfaction	• Definition according to [32]. NRS from 0 (= dissatisfied) to 10 (= very satisfied) (see **Fehler! Verweisquelle konnte nicht gefunden werden.**) for patients/residents with MMSE [29] scores of 24 or higher • Means	Days 0, 2, 4, 6, 8, 10, 12, 14	• **Patient satisfaction:** 0 - 10 [numeric]
IAD related Itch	• Patient reported IAD related itch	Days 0, 2, 4, 6, 8, 10, 12, 14	• Presence of IAD related itch (0) No (1) Yes

Outcome Name	Device/Measurement instrument/Scale and metric	Time points	Response Options/Categories/ Range
Safety	• Local intolerances according to [34] • 5-Item-Scale (ordinal)	Days 0, 2, 4, 6, 8, 10, 12, 14	• **Presence of Local intolerances:** (0) None; (1) homogeneous redness with scattered papules; (2) homogeneous redness and homogeneous infiltration (3) homogeneous redness and infiltration with vesicles (4) homogeneous redness and infiltration with coalescing vesicles
	• **Adverse Events (AEs):** According to the definition of the EU regulation 2017/745 Medical Device Regulation (MDR) Article 2 (57) • **Serious Adverse Events (SAEs**): According to the definition of the EU regulation 2017/745 MDR Article 2 (58) • **Incidents:** According to the definition of the EU regulation 2017/745 MDR Article 2 (64) • **Serious incidents:** According to the definition of the EU regulation 2017/745 MDR Article 2 (65)	Day 0, Day 2, Day 4, Day 6, Day 8, Day 10, Day 12, Day 14	• SAEs according to the definition of the EU regulation 2017/745 MDR Article 2 (58) will be documented on separate reporting forms (see **Fehler! Verweisquelle konnte nicht gefunden werden.**) • Incidents and Serious Incidents according to the definition of the EU regulation 2017/745 MDR Article 2 (64) and (65) will be documented and reported to the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)

Outcome Name	Device/Measurement instrument/Scale and metric	Time points	Response Options/Categories/ Range
Feasibility	• Willingness to participate (proportion of participants from all eligible patients, reasons for non-participation)		• **Percentage of persons from the eligible population who are willing to participate:** xx [%] • **Reasons for declining participation:** (1) Feel too old or too ill to participate (2) Perceive study participation as a burden (3) Do not want additional/ other treatment (4) Do not see benefits in participating (5) Not interested in research (6) Do not want to be randomly assigned to a treatment (7) Not interested (reason not specified) (8) Other [free-text]
Adherence/ compliance to prescribed intervention	• Number of applied skin care procedures per day according to diary		• Percentage of completely/ correctly documented days: xx [%] • Number of used products xx [quantity]

2.7.1 INITIAL SKIN ASSESSMENT

At the baseline visit on day 0, a skin assessment is performed to check and document the initial condition of the skin in the study area. It will be documented whether an IAD (classified according to GLOBIAD [25]) is already present and if the skin is intact or eroded (according to *Proceedings of the Global IAD Expert Panel* [35]). Other dermatological conditions in the study area will also be documented.

Study participation with pre-existing IAD is only possible if it is a mild form with early signs of IAD and intact skin (GLOBIAD category 1 A). If the initial skin assessment reveals a moderate or severe form (including skin loss or clinical sign of infection) of IAD (GLOBIAD category 1 B; 2 A or 2 B), the participant will be excluded. Other dermatological conditions or skin affections (at investigational areas of the skin) requiring dermatological treatment or interfering with the conduct of the study also lead to exclusion.

2.7.2 MEXAMETER MEASUREMENT

The erythema level will be measured with a modular system consisting of the *Mexameter® MX 18* probe, connected to the basic device *Multi Display Device (MDD) 4* (Courage + Khazaka, Cologne, Germany). The probe measures the haemoglobin (erythema) components of the skin, which are mainly responsible for its color. The measuring principle is based on absorption and reflection. For the measurement, the probe emits light with three specific wavelengths and a receiver unit measures the reflected light from the skin. As the quantity of emitted light is standardized, it is possible to calculate the quantity of light absorbed, by measuring the light reflected by the skin. Values are displayed in device-specific arbitrary units (AU) and range from 0 AU to 999 AU, whereby higher readings indicate more extreme erythema.

2.7.3 RESIDENT/PATIENT REPORTED OUTCOME MEASURES

Participants are asked if IAD related itch is present or not. IAD related pain will be assessed with a numeric rating scale (NRS) from 0 (= no pain) to 10 (= worst possible pain) (**Fehler! Verweisquelle konnte nicht gefunden werden.**) for patients/residents without cognitive impairment (according to Mini-Mental-State-Examination (MMSE) [29] (**Fehler! Verweisquelle konnte nicht gefunden werden.**) with scores of 24 or higher). For patients/residents with dementia (according to MMSE [29] scores of < 24) the Pain Assessment in Advanced Dementia (PAINAD-G) [30, 31] scale will be used (**Fehler! Verweisquelle konnte nicht gefunden werden.**). Patient satisfaction is assessed by

NRS from 0 (= dissatisfied) to 10 (= very satisfied) (**Fehler! Verweisquelle konnte nicht gefunden w erden.**) for patients/residents with MMSE [29] scores of 24 or higher. Definition according to [32].

2.7.4 PARTICIPANTS TIMELINE

In total, eight study visits are planned. After inclusion, residents will be followed-up for 14 days. Written informed consent will be obtained prior study participation by the residents/patients themselves or their legal representatives, if applicable. Demographic information (e. g. age, sex, care level), incontinence type according to medical records, medical information (e. g. relevant main medical diagnoses and relevant regular medication) and further care specific data is collected for all participants. A detailed list of variables and how they will be collected (e. g. device/instrument/scale and metric as well as measurement time points) is shown in Table 4. The planned trial flow is shown in Figure 1 and a schematic overview of the detailed study schedule for the individual participants is shown in Table 3.

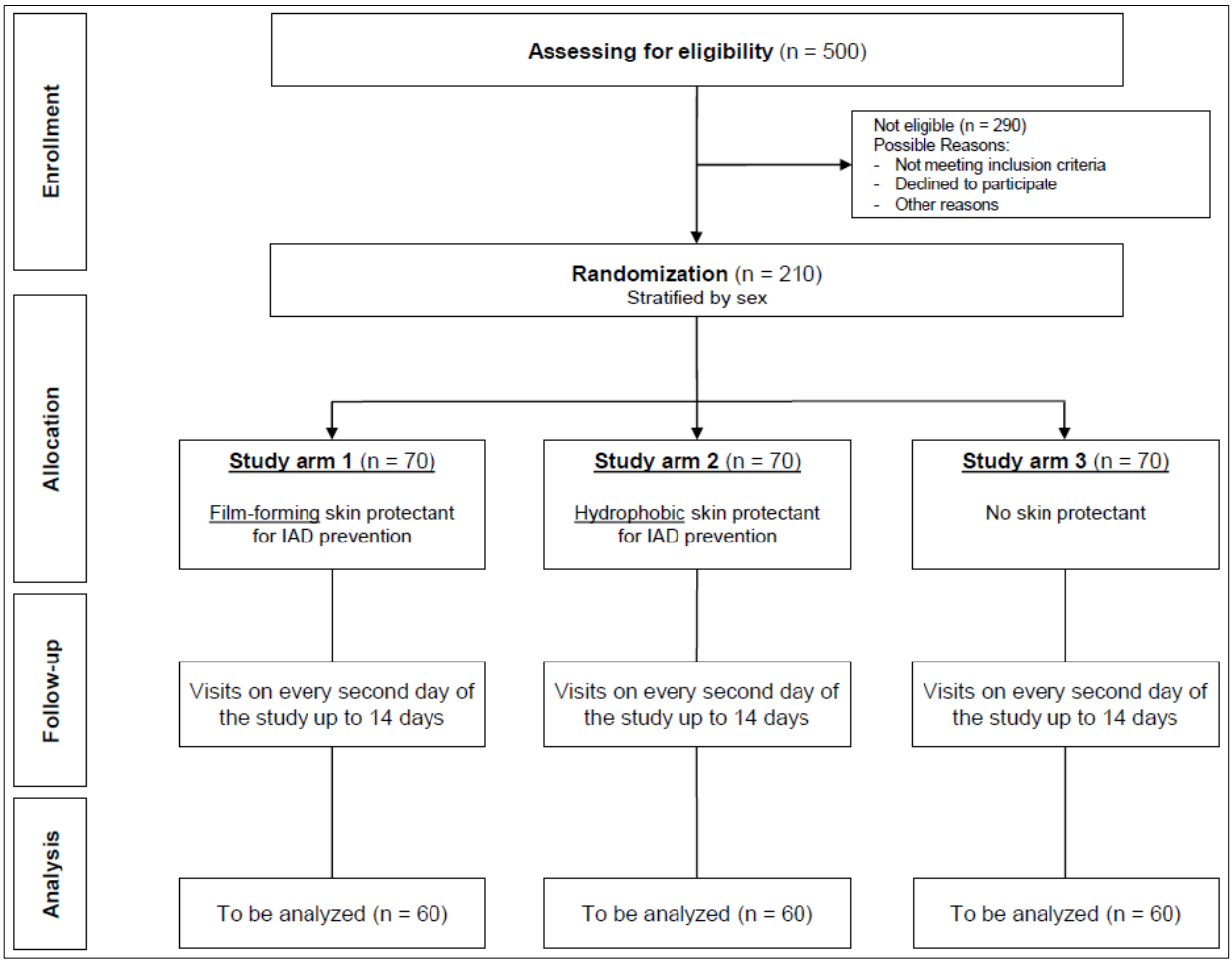


Figure 1: Overview of the planned trial flow.

Table 3: Study schedule for individual participants.

	Days														
	Enrollment	**Allocation**	**Post-allocation**												**Close-out**
Timepoint	**-5 to 0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Formal requirements and allocation																
Eligibility screening	x															
Informed consent	x															
Randomization and allocation		x														
Participant characteristics																
Demographic variables (e.g. age, sex, care level)		x														
Relevant medical diseases		x														
Relevant medications		x														
Physical function (Barthel-Index)		x														
Cognitive status (MMSE)		x														
Incontinence characteristics		x														
Clinical skin assessment																
Gent Global IAD categorization (GLOBIAD)		x		x		x		x		x		x		x		x
Erythema (visual inspection)		x		x		x		x		x		x		x		x
Erythema (instrumental measurement)		x		x		x		x		x		x		x		x
Erosion		x		x		x		x		x		x		x		x
Maceration		x		x		x		x		x		x		x		x
IAD-related pain (NRS or PAINAD-G)		x		x		x		x		x		x		x		x
IAD-related itch		x		x		x		x		x		x		x		x
Patient satisfaction (NRS)		x		x		x		x		x		x		x		x
(Serious) Adverse Events or Incidents		x		x		x		x		x		x		x		x
Interventions and study-related procedures																
Study arm 1: Conduction of the standardized skin cleansing regime and application of the film-forming skin protectant		●	―	―	―	―	―	―	―	―	―	―	―	―	―	●
Study arm 2: Conduction of the standardized skin cleansing regime and application of the hydrophobic skin protectant		●	―	―	―	―	―	―	―	―	―	―	―	―	―	●
Study arm 3: Conduction of the standardized skin cleansing regime, no additional skin protectant		●	―	―	―	―	―	―	―	―	―	―	―	―	―	●
Other																
Skin care diary completed by nurses		●	―	―	―	―	―	―	―	―	―	―	―	―	―	●

2.8 Sample Size

2.8.1 Whole trial

Due to the exploratory nature of the trial, a formal sample size calculation is not applicable [23]. The trial has two strata (I) sex (male/female); (II) condition of the skin (no IAD vs. IAD Category I) and three study arms. Based on these conditions and following the recommendations for exploratory trials [36], a sample size of n = 60 participants per group is considered feasible and sufficient to describe group differences. In order to compensate a possible loss-to-follow-up, n = 70 patients per group will be included.

2.8.2 Interview Part

From the patients included in the trial, n = 12 participants (four participants per study arm) will be invited to participate in a qualitative interview. This number is based on the recommendations for doing qualitative research in feasibility studies for RCTs [22]. To identify possible sex-specific differences, two male and two female participants will be interviewed per study arm.

2.9 Recruitment

2.9.1 Institutional Level

Potentially eligible local nursing homes and geriatric hospitals or hospitals with geriatric wards will be contacted and invited to participate by letter, Email or phone. If the institution is interested in the project, an initial in-person meeting is arranged at the facility. Nursing homes and geriatric hospital wards are informed about the aims and scope of the project.

The following advantages or rewards will be offered to the nursing homes in case of participation:

(1) Certificate of participation if desired (e.g. for marketing purposes of the institution)
(2) Free in-house education (certificates of attendance for the employees if desired)
(3) Free educational materials (printed materials including booklets, handouts, posters)
(4) Free provision of skin cleansing and protection products as well as incontinence materials (including disposable wash mitts, incontinence pants) for participating residents/patients.

2.9.2 Participant Level

The recruitment of participants in the geriatric hospitals/wards and the nursing homes will be realized in close cooperation with the local responsible contact person on-site. The responsible contact person can either be the nursing home manager itself or a qualified person, delegated by the management, such as the nursing care manager. The responsible person in the institution will inform possible eligible residents/patients and hand out a first study information leaflet. Interested residents or their legal representatives will then be contacted by the study team in person and will be informed about the conduct of the study.

3. METHODS: ASSIGNMENT OF INTERVENTIONS

3.1 SEQUENCE GENERATION

A computer-generated, block-randomization with 1:1:1 allocation ratio per trial arm will be used. In order to detect any possible sex-related differences or interactions [37] the randomization will be stratified according to males and females. Two independent randomization lists are generated according to the same principle, one for participants in the geriatric hospitals/wards and one for the participants of the nursing homes. This is done to ensure that there is an equal distribution of allocation in both settings. Computerized random numbers will be generated by the statistician not involved in study planning or any further study-related procedures or the associated data analysis. The random number list is kept with the statistician until the end of the study.

3.2 ALLOCATION CONCEALMENT MECHANISM

The allocation will be conducted by the investigator using numbered opaque envelopes (GH-001 to GH-200 for participants in geriatric hospitals/wards; NH-001 to NH-200 for participants in the nursing homes) containing the computer-generated random numbers. The used envelopes are prepared by an employee who is not involved in the planning of the study, the associated data analysis, or any further study-related procedures.

3.3 BLINDING

Due to the nature of the intervention, involved caregivers and participants will not be blinded. In addition, the person of the study team who reviews the diaries and verifies the correct performance of study-related procedures by nurses is also not blinded. Because the diaries provide information about assignment to the study arm, blinding of the reviewer is not possible due to the given circumstances. In order to enhance the internal validity, every visit will be performed by two members of the study team.

Member 1 of the study team performs the following tasks:

- **(I)** Conduct of the study visit and its related tasks as listed in Table 3 under the section "Clinical skin assessment" (including assessment of IAD-related pain, itch, patient satisfaction as well as the instrumental measurement of the erythema). Member 1 **does not conduct** any part of the assessment regarding the condition of the skin, which includes GLOBIAD IAD categorization as well as the visual inspection of erythema, erosion and maceration.
- **(II)** Conduct of monitoring activities as described in Table 1 under the section "11. How well".

Member 2 ("outcome assessor") of the study team is blinded and does the skin condition-related assessments only (including GLOBIAD IAD categorization as well as the visual inspection of erythema, erosion and maceration). The blinded person documents the results of the skin assessment on a separate "Skin Assessment Data Collection Form" (see **Fehler! Verweisquelle konnte nicht gefunden werden.**), independently from the main CRF (see **Fehler! Verweisquelle konnte nicht gefunden werden.**). This procedure is necessary to prevent accidental unblinding of the outcome assessor by trial group-specific information collected in the main CRF. The Skin Assessment Forms will be reintegrated into the main CRF after the respective participant has completed the study or ended its participation.

The data manager will be blinded throughout the period of data entry and verification until data base closure. The trial statistician will be blinded during statistical analysis.

4. METHODS: DATA COLLECTION, MANAGEMENT, AND ANALYSIS

4.1 DATA COLLECTION METHODS

All data collectors will be trained in obtaining accurately the variables of interest (see 2.7 and 4.1.3). Paper source data (SD) and paper case report forms (CRFs) will be used to document all study variables of interest. SDs will include originals/copies/transcripts of resident-/patient-related records, physicians', nurses' and research assistans' notes, visit schedules, diaries, dispensing LOGS, signed ICFs other relevant reports.

All examinations, assessments, and measurements will be performed onsite in the participating geriatric hospitals/wards and nursing homes in the patients'/residents' room. Demographic characteristics and basic medical information such as main medical diagnoses and regular medication will be extracted from the master data records of the respective institutions. The skin assessments will be performed by an experienced and qualified member of the study team who, as a blinded outcome assessor, will be constantly vigilant to avoid accidental unblinding. Other assessments and the skin measurements will be conducted by trained members of the study team, which are not involved in the skin condition assessments (including GLOBIAD IAD categorization and visual inspection of erythema, erosion and maceration).

All study data has to be continuously documented in the CRFs and associated forms by the investigator or his authorized staff. Data entries have to be made by using a non-erasable blue or black ballpoint pen. Data corrections must be made in a way which does not obscure the original entry. The corrected data must be dated and initialed by the corrector. Predefined variables will be

entered into an eCRF provided by the CTO of the Charité meeting GCP standards (including personalized login and track change).

4.1.1 SKIN ASSESSMENT

The skin assessments visits will be performed at Days 0, 2, 4, 6, 8, 10, 12 and 14. This will be performed by GCP-trained members of the study team. Nursing home residents/patients in geriatric hospitals/wards will be assisted to undress at the area of interest. In close cooperation with the caregivers, this will be ideally combined with the scheduled regular general basic care procedures, clothing changes or medical procedures.

The variables regarding IAD categorization, erythema, erosion and maceration will be documented by the blinded assessor. In case that a dermatological/medical condition is detected which is, in the opinion of the assessor, incompatible with further study conduct, participation for this subject will be terminated with specification of the underlying reason

4.1.2 SKIN MEASUREMENTS

Erythema level measurements will be conducted at Days 0, 2, 4, 6, 8, 10, 12 and 14 in duplicates at the cranial end of the gluteal cleft. Study team members will conduct the measurements according manufacturer's instruction manual (**Fehler! Verweisquelle konnte nicht gefunden werden.**; **Fehler! Verweisquelle konnte nicht gefunden werden.**) and the respective SOP (see **Fehler! Verweisquelle konnte nicht gefunden werden.**). All study team members who perform the measurements will have a documented training prior to the study and undergo a brief examination to ensure similar measurement performance. Used measurement devices will be calibrated and serviced periodically according to the manufacturer instructions.

4.1.3 OTHER TRIAL DATA

Other collected trial data are shown in-Table 4.

Table 4: Other trial data

Variable Name	Device/Measurement instrument/Scale and metric	Time points	Response Options/Categories/Range
Demographics			
Age	• Age in years	Day 0	XXX [years; numeric]
Sex	• Obtained from medical record	Day 0	(1) Male (2) Female
Care level	• Obtained from medical record in nursing homes • According to Volume XII of the German Social Security Code (SGB XII), defined by § 61b SGB XII	Day 0	(1) none; (2) Grade 1 (3) Grade 2 (4) Grade 3 (5) Grade 4 (6) Grade 5
Smoking status	• Smoking status according to participant's statement	Day 0	• **Smoking status:** (1) Smoker (2) Non-smoker
Body height	• Obtained from medical record • Height in cm	Day 0	XXX [numeric]
Body weight	• Obtained from medical record • Weight in kg	Day 0	XXX [numeric]
BMI	• Calculated from body weight and body height • BMI = kg/m^2		XX [numeric]
Skin phototype	• According to Fitzpatrick classification	Day 0	(1) Skin Type I; (2) Skin Type II; (3) Skin Type III; (4) Skin Type IV; (5) Skin Type V; (6) Skin Type VI
Medical History/ Functional Assessments			
Main medical diagnoses	• Relevant main diagnoses obtained from medical records	Day 0	• **Main medical diagnosis** 1. Hypertension 2. Dementia 3. Renal failure 4. Diabetes mellitus 5. Heart arrhythmia

Medications	• Relevant medications obtained from medical records	Day 0	• **Category of medication** (1) Antithrombotic medication (2) Beta-adrenoreceptor antagonists (3) Diuretics (4) Medication influencing the renin-angiotensin (5) Psychoanaleptics (6) Antibiotics
Cognitive Ability	• Assessed with the MMSE • Score range: 0 to 30	Day 0	(1) ≥ 24 (Normal cognition; no dementia) (2) 19 to 23 (Mild dementia) (3) 10 to 18 (Moderate dementia) (4) 9 and lower (Severe dementia)
Physical function	• Barthel – Index • Score range: 0 to 100 • Means	Day 0	• Item 1: Feeding (0; 5 or 10 points) • Item 2: Bathing (0 or 5 points) • Item 3: Personal toilet (0 or 5 points) • Item 4: Dressing and undressing (0; 5 or 10 points) • Item 5: Controlling bowels (0; 5 or 10 points) • Item 6: Controlling bladder (0; 5 or 10 points) • Item 7: Toilet use (0; 5 or 10 points) • Item 8: Transfer (bed to chair and back) (0; 5; 10 or 15 points) • Item 9: Standing up and Mobility (0; 5; 10 or 15 points) • Item 10: Ascend and descend stairs (0; 5 or 10 points)
Diarrhoea	• Interview by study assistant or obtained from medical records	Day 0	• Diarrhoea (0) No (1) Yes
Urinary tract infection	• Interview by study assistant or obtained from medical records	Day 0	• Urinary tract infection (0) No (1) Yes

Demographic variables (age, sex, care level,), main medical diseases, medications and, if possible, Barthel-Index scores will be obtained from medical records by trained study assistants. Data regarding incontinence will be obtained from the medical records or if possible via interview of the participants or the responsible caregiver.

A possible cognitive impairment will be rated using the MMSE [29]. Only residents with a score of 24 or higher will receive the questionnaires regarding itch, pain and patient satisfaction. A functional assessment using the Barthel-Index will be conducted by study assistants, if this has not already been done by the nursing home. The Barthel-Index measures physical function related to the daily activities using ten items (e.g. washing and toilet use, eating and mobility or incontinence). Scores ranges from 0 (= very dependent) to 100 (= not dependent) [38].

4.2 DATA MANAGEMENT

A paper SD file will be created for the study. Data (informed consent process and consent retrieval, demographics, medical history, skin assessments, skin measurements, clinical scores, rating scales) will be collected during the study visits in written form. An eCRF will be developed by the CTO. Data from the SD will be extracted and entered into an eCRF. The investigator agrees to maintain accurate CRF and source documentation as part of the research under this protocol. Data management and handling of data will be conducted according to the trial specific Data Management Plan (DMP) of the CTO in accordance with ICH guidelines.

Data entry will be performed by the trial site personnel. Validation and data queries will be handled by the data management team of the study. According to a pre-defined query process changes to data entries in the eCRF (if any) will be made at the site by the qualified trial site personnel. The eCRF will have an audit trail with appropriate functionality for data capture, tracking and documentation of any queries or changes. Electronic signatures will be used to verify the data and identify the person entering or changing the data (SecuTrial).

After all data management activities (query and cleaning process) are completed, the database will be locked and exported as SPSS datasets. Any deviations, i.e. discrepancies and additions from the process defined in the DMP, will be described in a trial specific data management report.

4.3 STATISTICAL METHODS

All statistical evaluations will be conducted using the statistical programming language R and IBM SPSS statistics.

Variables will be described for each setting (geriatric hospitals/hospital wards and nursing homes) and individual level on an intention-to-treat (ITT) basis. Outcomes will be described using means, medians, proportions (including the cumulative incidence) and corresponding spread estimates per group. Mean differences between groups and time points will be calculated. In addition, we will provide Kaplan-Meier curves for the time from inclusion in the study to the onset of IAD in the three study groups. The observations are censored if patients withdraw from the study before the onset of an IAD or if the study is terminated before the onset of an IAD. Because this is an exploratory trial no group comparisons using formal statistical tests will be performed. However, we will calculate two-sided 95% confidence intervals for all means and proportions and for the differences in means and proportions between the three study groups. All statistical analyses will be performed for the whole sample and for both sex strata separately.

The interviews and free text responses will be analyzed using qualitative methods including labelling, coding, and inductive outcome extraction.

4.4 Analysis population

The statistical analysis will be based on the ITT principle, this includes the whole study population and is considered as the 'full analysis set'. The IIT analysis bases on the initial treatment intent. The analysis contains all participants that met the inclusion criteria and were randomized, irrespective of possible protocol deviations, discontinuation of the study treatment or withdrawal from the study by the subject. Participants that die, discontinue participation or leave the institution during the study period will be analyzed until that time point (early termination). As only exception, the following reasons cause an exclusion of participants from the full analysis set: (I) No treatment was applied at all or (II) there are no data available after the subject's randomization. Subjects excluded from the full analysis set will be mentioned in the study report and reasons for exclusion will be documented per group. In case of consent withdrawal, all subject's data collected until this time point will remain part of the study database and may not be removed. This will be clearly stated in the ICF.

An additional per protocol (PP) analysis will be performed. The parameters for inclusion in the PP analysis set are defined as follows: **(I)** Participants that completed the study without major protocol deviations or violations (i. e. wrong product/incorrect application, missing application for more than 72 h, more than three missing study visits, inclusion/exclusion criteria not met) and **(II)** terminated the study regularly (study participation of at least 7 consecutive days). For all subjects included in the full analysis set but not in the PP set, the reason for exclusion will be stated in the

study report per group. As the ITT analysis is intended to preserve the original randomization and to avoid potential bias due to exclusion, the PP analysis aims to analyze the possible effects of the intervention administered under optimal conditions. Therefore, both analyzes are a necessary component to determine the feasibility of the applied procedures as well as possible effects of the intervention. Especially with regard to planning of a subsequent confirmatory trial.

5. METHODS: MONITORING

5.1 DATA MONITORING

A clinical trial advisory board (CTAB) will be implemented. It consists of national and international experts in the field of dermatology, geriatrics and nursing science. Further, representatives of the German Incontinence Support Group (Deutsche Inkontinenz Selbsthilfe e.V.) will be part of the CTAB, representing the interests of the nursing home residents and patients. The support group will invite incontinent patients to be part of the study committee. A meeting will be held in which the background and aims of the study were presented and the general aspects of the planning, implementation and analysis of the study were explained. The CTAB will then actively participate in full clinical trial protocol development, review and supervision of the study progress.

Monitoring of the study is the responsibility of the Investigator and is delegated to CTO. The monitor is responsible for reviewing the progress of the study, verifies the adherence to the protocol as well as compliance to ICH-GCP. The monitor works according to the SOPs of the CTO. The monitor will visit the center before, during, and after completion of the study to ensure that the study is conducted, recorded, and reported according to the protocol. During the on-site visits, parts of the eCRF will be reviewed for completeness with corresponding SDs. As part of the data audit, SDs will be made available for review by the study monitor. The study monitor may periodically request review of the ISF to ensure completeness of documentation in all respects of study conduct. The monitor may verify the participation of an institution via phone call with the responsible contact person of the nursing home/ hospital/ hospital ward.

5.2 ELECTRONIC DATA CAPTURE

Data entry

The CTO uses secuTrial® - a Remote Data Entry (RDE) software solution of interActive Systems (iAS) - to capture trial data and transfer them to a central database. SecuTrial® is in compliance with the regulatory standards (FDA CRF 21 Part 11 and GCP) and contains the required features like audit trail, assigned roles and rights of study employees, management concept and electronic signatures.

The system provides the eCRF which allows the documentation of trial data online at any time by using a standard internet browser (e.g. Chrome, Firefox, Opera, etc.). Furthermore the eCRF contains functions to perform plausibility, consistency and range checks of the entered data to get a high level of data quality. Access to the eCRF is person-specific and password protected. All access rights (read or enter data) will be defined depending on their function in the trial (principle or clinical investigator, study assistant etc.).

The communication between the client-PC and the trial database on the server is based on the secure data-transfer-protocol (SSL - Secure Sockets Layer). This will prevent any illegal access to the trial data by unauthorized parties.

Query Management

There is a Query management tool as an integrated part of the RDE system. This tool allows the communication between the CTO and the clinical investigator at the site. In case of uncertainties, errors or improper data, the CTO or the monitor can set queries to clarify the affected question.

5.3 HARMS

One investigational product for skin protection is ' ESENTA™ Hautschutz Spray' (PZN: 16866747). It is CE certified in accordance with Article 20 (1) of Regulation (EU) 2017/745. The investigational product is used and evaluated within its defined intended purpose in the context of the planned clinical trial. Therefore, its use is considered safe and the use of the investigational product does not impose any additional burden on the participants. The other product used for skin protection is 'Hydrophobes Basisgel DAC'. It may be regarded as a cosmetic product according to the EU Regulation No 1223/2009 on cosmetic products.

5.3.1 DEFINITION OF ADVERSE EVENTS AND INCIDENTS

Long-term care residents and patients in acute care are affected by a variety of diseases and medical problems. Therefore, the Adverse Events (AEs) and Serious Adverse Events (SAEs) terminology (according to EU regulation 2017/745 MDR Article 2 (57) and (58)) will be adopted for this trial.

Adverse Event

An AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of the clinical investigation, and is related to the investigational device.

The observation period for AEs begins at the time the resident/patient gives informed consent and continues until the study is completed. All residents experiencing AEs will be monitored

until symptoms subside, or until there is a satisfactory explanation for the changes observed. If the interval between two episodes of an AE is less than seven days, these episodes will be counted as one AE.

The investigator will be responsible for the necessary acute medical treatment of any adverse event that occurs during the trial and that is related to the investigational product. The investigator ensures that appropriate medical care is also provided thereafter, if necessary.

Serious Adverse Event

Serious Adverse Event (SAE) means any AE that led to any of the following:

(a) death,
(b) serious deterioration in the health of the subject, that resulted in any of the following:
    (i) life-threatening illness or injury,
    (ii) permanent impairment of a body structure or a body function,
    (iii) hospitalization or prolongation of patient hospitalization,
    (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
    (v) chronic disease

Hospitalization solely for the purpose of diagnostic tests, even if related to an AE, elective hospitalization for an intervention which was already planned before the inclusion of the resident in the clinical study, and admission to a day-care facility may not themselves constitute sufficient reasons to be considered as a SAE.

Incident

“An 'incident' means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect” (EU regulation 2017/745 MDR Article 2 (64))

Serious Incident

"A ‘serious incident’ means any incident that directly or indirectly led, might have led or might lead to any of the following:

(a) The death of a patient, user or other person,
(b) The temporary or permanent serious deterioration of a patient’s, user’s or other person’s state of health,
(c) A serious public health threat"

(EU regulation 2017/745 MDR Article 2 (65))

5.3.2 Incident Reporting

(Serious) incidents must be documented in an incident report form (available online from BfArM) and reported via online platform to the BfArM.

5.4 Auditing

The BMBF or its representatives may perform audits or inspections.

6. Ethics and Dissemination

6.1 Research ethics approval

The study was developed and will be conducted in accordance with the principles stated in the Declaration of Helsinki and subsequent amendments and in accordance with the Guidelines for Good Clinical Practice (ICH Topic E 6 (R1)).

An ethical approval application together with the ICF, study information and any other requested documentation has been submitted to the responsible EC of the Charité - Universitätsmedizin Berlin. The study received EC approval on 07.04.2022 (EA4/043/22).

6.2 Protocol amendments

Substantial amendments to the protocol will be submitted to the EC. The investigator is responsible for informing the EC of all problems involving risks to residents. If changes in the ICF become necessary, these documents must be submitted to the EC as well. Changes will be filed in the ISF.

6.3 Consent or assent

The investigator is obliged to give full written and verbal information to the residents/patients and if applicable their legal representatives about the nature of the study, its purpose, the procedures involved, the expected duration, potential risks and discomforts as well as about the right to discontinue participation in the study without affecting their further relationship with the investigator or their future care.

Prior to inclusion into the study, the consent for each participating subject must be obtained on a written statement (ICF) which is approved by the EC. The ICF has to be written in national language and an easily understanding target group adapted wording has to be used. Two original ICFs must be personally dated and signed by the residents/patients or if applicable by their legal representatives. In all cases, the Investigator must also personally date and sign the original ICFs and confirm by this way that he/she has provided all information regarding this study. One original is intended for the resident/patient and the other one for the ISF.

The signed ICF must be obtained before engaging any study-related procedure with the resident/patient or data collection. The information and consent procedure is the responsibility of the investigator. The investigator can delegate qualified study team members to obtain the informed consent.

6.4 INSURANCE

All subjects enrolled in this study are covered against negligent conduct of the Investigator or study assistants by the liability insurance of the Charité - Universitätsmedizin Berlin.

6.5 CONFIDENTIALITY AND DATA PROTECTION

All personal information about potential and enrolled participants is confidential. This ensures the strictly split between the personal data and participant-related dataset (trial data).

A pseudonym is generated for every new participant. The pseudonym will be a combination of two characters (GH for participants in geriatric hospitals/wards; NH for participants in the nursing homes) and three numbers with ascending sequence (001 to 250). All trial data of the resident will be linked with this pseudonym. Personal data of the resident will not be saved in the trial database at any time.

The investigator affirms and upholds the principle of the participant's right to protection against invasion of privacy. Throughout this study all data recorded or passed on for further evaluation will be coded by the randomization number. Identification is restricted to authorized persons. Participant's data may be stored and electronically processed by the investigator for a scientific purpose. This study will comply with the requirements of the Berliner Datenschutzgesetz (BlnDSG), the General Data Protection Regulation (GDPR; EU 2016/679) and the Kirchengesetz über den Datenschutz der Evangelischen Kirche in Deutschland (EKD).

6.6 DECLARATION OF INTERESTS

The principal investigator declares, that he has no financial or competing interests for the overall trial.

6.7 ACCESS TO DATA

All study-related information will be stored securely at the Institute for Clinical Nursing Science. All information regarding the participants will be stored in locked file cabinets in areas with limited access. Electronically data (e.g. photographs) are stored on a secured digital server of the Institute for Clinical Nursing Science.

The investigator:

1. Ensures that the study is conducted in accordance with the protocol and the applicable ethical and regulatory requirements and that all data generated during the study are accurate, relevant and valid and are entered into the SD;
2. Keeps an ISF in order to ensure filing and subsequent archiving of all relevant study documents during and after the study (original protocol, ethics committee approval and administrative documents, etc.);
3. Retains a subject identification list containing the participants names, addresses and randomization numbers to allow checking of data reported on CRFs with those from SD;
4. Enables direct access to SDs for monitoring, audits and inspections, thus ensuring accuracy of the data (if applicable). All representatives that have been granted access to the data documentation to perform quality monitoring/audit keep professional confidentiality with regards to the participant's data.

The Investigator is responsible for ensuring that all study records, including SD, ISF, signed ICFs, and the subject identification list are archived for the period of time required by law.

6.8 ANCILLARY AND POST-TRIAL CARE

Ancillary and post-trial care will not be provided.

6.9 DISSEMINATION POLICY

Results dissemination will start with registration at Clinicaltrials.gov and at the DRKS before enrollment of the first participant. In addition, the trial protocol will be published in the journal 'Trials' or any other comparable open access journal. After study completion, results will be uploaded at clinicaltrials.gov and published in international journals and at least in one German journal (e.g. 'Pflege'). All articles will be published open access. Results will be further presented at national and international conferences. To support dissemination of the trial results for subsequent research purposes (e.g. individual-patient data (IPD) meta-analyses or secondary analyses), we will provide access to anonymized IPD from this trial according to the recommendations of the International Committee of Medical Journal Editors (ICMJE) [39]. It is planned to share the data at zenodo.org supported by the European Commission.

VI. REFERENCES

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Comparison of two skin protection regimes for the Prevention of Incontinence-associated Dermatitis in geriatric care: An exploratory trial Acronym: PID

DRKS00028954

Statistical Analysis Plan

Version *04, 04/17/2025*

Intervention therapy:	**Intervention arm I**: Standardized mild skin cleansing regimen and daily topical application of a film-forming skin protectant at the exposed skin areas. **Intervention arm II**: Standardized mild skin cleansing regimen and daily topical application of a hydrophobic skin protectant at the exposed skin areas.
Control therapy:	Standardized mild skin cleansing regimen without application of an additional skin protectant
Study population:	Incontinent geriatric patients
Sponsor:	Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany
Financial support:	Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung (BMBF)) by grant number 01KG2020.
Protocol registry identification:	DRKS00028954
Clinical phase:	Randomized controlled, parallel group, three-arm, assessor-blinded exploratory trial

Approved by

Prof. Dr. rer. cur. Jan Kottner
Name, *Principal Investigator*

Place, Date, Signature

Dipl.-Math. Maximilian Mönch
Name, *Statistician*

Place, Date, Signature

PD Dr. phil. Ulrike Grittner
Name, *Statistician*

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Dr. rer. medic. Monira El Genedy-Kalyoncu
Name, Trial Coordinator

Place, Date, Signature

File history

Version	Date	Major changes	Comment
01	01/14/2025		Initial SAP
02	03/20/2025	• Erythema level 1 and 2 reporting	The mean of Erythema levels 1 and 2 will be aggregated and analyzed as endpoint
		• Exclusion of feasibility assessment	The percentage of eligible individuals who were willing to participate could not be assessed.
		• Analysis of erosion: no adjustment for baseline	Erosion at baseline was exclusion criterion
		• Correction of cognitive condition for patient satisfaction assessment	If IAD present and MMSE ≥ 24
		• Specification of timepoints for secondary outcome assessments	If IAD present
		• Addition of location (front/back) for subgroup analyses	For Erosion
			Remark: additional minor changes (formatting, spelling and grammar)
03	04/15/2025	• Flow chart adjustment	The flow chart was modified and now includes updated information on participant flow, and exclusions; starting from the set of included subjects.
		• Enumeration of participating wards	The number of nursing homes and the respective participant counts have been added
		• Clarification on patient satisfaction measurement	Patient satisfaction was measured at each visit day if MMSE ≥24, regardless of IAD presence
			Remark: additional minor changes (formatting, clarifications)
04	04/16/2025	• Adding the secondary analysis for patients with no initial IAD	Additional subgroup analysis
			Remark: additional formatting

Abbreviations

AE	Adverse Event
BlnDSG	Berliner Datenschutzgesetz
BMBF	Bundesministerium für Bildung und Forschung
BMI	Body Mass Index
CRF	Case report form
CTO	Clinical Trial Office at the Charité
DMP	Data management plan
DRKS	Deutsches Register Klinischer Studien (German Clinical Trials Register)
DSGVO	Datenschutzgrundverordnung (General Data Protection Regulation)
EC	Ethics committee
EU	European Union
eCRF	Electronic case report form
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GDS	Global Deterioration Scale
GLOBIAD	Ghent Global IAD Categorization tool
IAD	Incontinence associated dermatitis
ICD	International Classification of Diseases
ICF	Informed consent form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IPD	Individual patient data
ISF	Investigator Site File
IIT	Investigator Initiated Trial
ITT	Intention-to-treat
MDR	Medical Device Regulation
MPDG	Medizinprodukterecht-Durchführungsgesetz
NRS	Numeric Rating Scale
PU	Pressure Ulcer
QoL	Quality of life

RDE	Remote Data Entry
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Source documents
SGB	Sozialgesetzbuch (Codebook of Social Law)
SOP	Standard operating procedure
SPSS	Statistical Package for the social science
SSL	Secure Sockets Layer
WHO	World Health Organization

1 Background

Incontinence-associated dermatitis (IAD) is an unwanted skin condition which is common in incontinent individuals. It is an inflammatory skin response due to repeated or prolonged contact with urine and/or stool [1, 2]. It can occur throughout the lifespan; thus, it is present in babies and young children ("diaper dermatitis") as well as in the older individuals [1].

The prevalence of incontinence rises with increasing age [3]; therefore, IAD is more common in aged populations. IAD prevalence is 3% to 23% in long-term geriatric care and 15% to 40% in acute care settings [4]. A representative prevalence study in institutional geriatric long-term care facilities showed an IAD prevalence of 35.4% [5, 6]. Thus, around one in three residents was affected by some form of IAD.

Clinically, IAD is manifested by skin redness, vesicles, nodular thickening and maceration of the tissue as well as defects of the skin up to the loss of the upper skin layers. For those affected, this can be a physical as well as psychological burden. In addition to pain, burning, and itching, IAD is associated with an increased risk of secondary infections and the development of pressure ulcers (PUs) [7, 8]. As a result of these changes, affected individuals may also suffer from a reduced quality of life, for example, through a loss of independence, reduction of social activities, or poor sleep due to IAD-related pain or itch [6, 9, 10].

With approximately 80%, the majority of residents in geriatric long-term care facilities, as well as a high proportion of geriatric patients in acute care settings, are affected by one form of incontinence and are therefore at potential risk of developing IAD [11-13]. If adequate preventive measures are taken at an early stage, IAD might be avoided. However, the high prevalence of IAD in these settings indicates that current prevention strategies are not optimal. Due to a lack of knowledge, the current nursing practices in the context of IAD prevention are mainly influenced by individual traditions and personal preferences and are not evidence-based [14]. At the same time, a clear need for support as well as assistance is expressed on the part of nurses and other caregivers in order to be able to perform an efficient and effective IAD prevention [15]. Therefore, it is an important aim to close existing evidence gaps in this area to support nurses and other caregivers with a solid scientific base for IAD prevention. The planned trial aims a direct comparison of the two most important skin protection product categories in the form of an explorative randomized controlled trial (RCT), taking core outcomes for IAD research into account.

1.1 Trial objectives

1.1.1 Primary objective

The primary research objective is to compare the incidence of IAD in two intervention groups and one control group and to estimate effect sizes for a possible subsequent confirmatory RCT.

1.1.2 Secondary objectives

Additional objectives are to test the feasibility of conducting a confirmatory RCT to prevent IAD and to evaluate the feasibility of measuring the Core Outcome Domains for IAD trials.
The trial will answer the following research questions:

- What are the effect sizes of the outcomes when comparing the intervention groups and the control group?
- Is the implementation of a standardized skin protection regime for the prevention of IAD feasible in geriatric hospital wards and nursing homes?
- Does the implementation of a standardized skin protection regime for the prevention of IAD reduce IAD-related itch and IAD-related pain?
- Is the measurement of Core Outcome Domains for IAD trials feasible?

1.2 Trial design

The trial is designed as a randomized controlled (ratio 1:1:1), parallel group, three-arm, assessor-blinded exploratory trial. Patients are randomized stratified by sex (male/female) into the treatment arms.The study was conducted in geriatric hospitals/geriatric wards of participating hospitals and in institutional long-term care facilities of the federal state of Berlin, Germany.

2 Analysis sets

2.1 Definitions

Intention-to-treat/Full analysis population

The full analysis set (FAS) contains all participants that met the inclusion criteria and were randomized, irrespective of possible protocol deviations, discontinuation of the study treatment or withdrawal from the study by the subject. Study participants will be categorized according to the intended treatment. As only exception, the following reasons cause an exclusion of participants from the full analysis set: (I) No treatment was applied at all or (II) there are no data available after the subject's randomization. Subjects excluded from the full analysis set will be mentioned in the study report and reasons for exclusion will be documented per group. In case of consent withdrawal, all subject's data collected until this time point will remain part of the study database and may not be removed.

Per protocol population

The per protocol (PP) set is defined as follows: (I) Participants that completed the study without major protocol deviations or violations (i. e. wrong product/incorrect application, missing application for more than 72 h, more than three missing study visits, inclusion/exclusion criteria not met) and (II) terminated the study regularly (study participation of at least 7 consecutive days).

For all subjects included in the full analysis set but not in the PP set, the reason for exclusion will be stated in the study report per group.

Safety analysis set

The safety population comprises all patients. Due to blinding, it doesn't matter whether they received one dose of the product or not.

Nr.	Inclusion criteria	Variable name	Comment
1	Geriatric patients or residents (≥ 65 years) staying/living in one of the participating institutions	sc_0080, sc_0091	sc_0091 for age; see sc_0020 at mnppid_visit for detailed info
2	Being incontinent of urine and stool	sc_0100	
3	Expected minimum length of stay of 14 days	sc_0110	
4	Intact skin with no clinical signs of IAD **or** intact skin with early clinical signs of IAD but without clinical signs of infection (GLOBIAD category 1 A	sc_0121	Check sc_0122 for IAD category
5	Written informed consent	sc_0130	
Nr.	**Exclusion criteria**	**Variable name**	**Comment/Analysis**
1	Residents/patients at the end of life	sc_0140	
2	Residents/Patients with skin loss due to IAD (GLOBIAD category 2 A) and/or signs of clinical infection in the IAD area (GLOBIAD category 1 B or2 B)	sc_0150	
3	Any other skin condition or wounds (at investigational areas of the skin) requiring additional treatment (including but not limited to pressure ulcers, intertrigo, infection)	sc_0160	
4	Known hypersensitivity or allergy to silicones and/or topical leave-on products	sc_0170	
5	Topical treatments in the IAD area.	sc_0180	

2.2 Application

The primary efficacy analysis will be done using the FAS including estimated values from multiple imputations for missing values (ITT framework). Participants that die, discontinue participation or leave the institution during the study period will be analyzed until that time point (early termination).

An additional analysis of the primary efficacy variable in the PP analysis set will be used as sensitivity analysis. The safety analysis includes calculation of frequencies and rates of adverse and serious adverse events in the safety analysis set.

As the ITT analysis is intended to preserve the original randomization and to avoid potential bias due to exclusion, the PP analysis aims to analyze the possible effects of the intervention administered under optimal conditions. Therefore, both analyzes are a necessary component to determine the feasibility of the applied procedures as well as possible effects of the intervention. Especially with regard to planning of a subsequent confirmatory trial

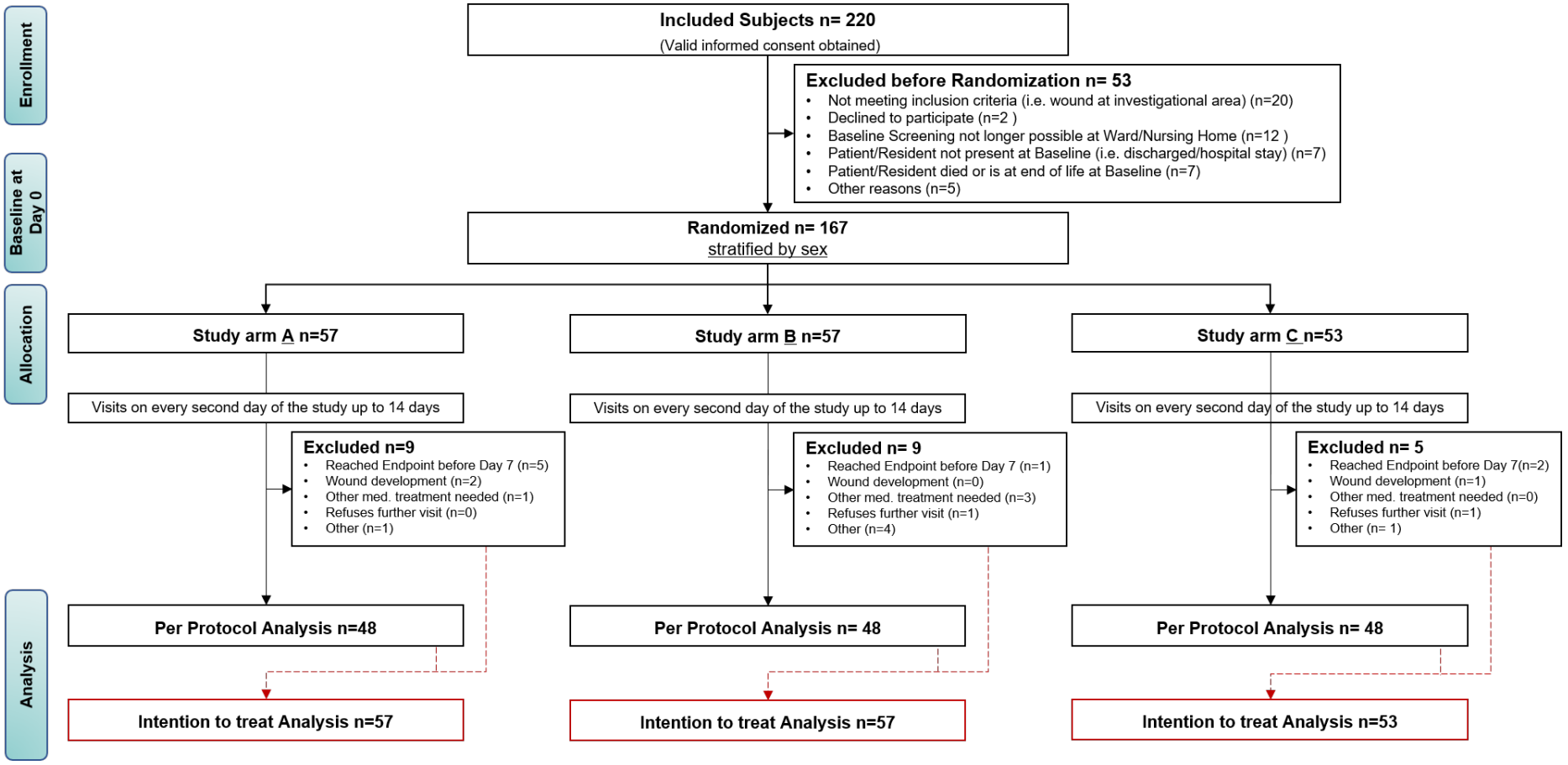
3 Trial centres

The study was conducted in geriatric hospitals/geriatric wards (acute care setting) of participating hospitals and in institutional long-term care facilities (nursing home setting) of the federal state of Berlin, Germany with a recruitment of n = 220 patients. Of these, 25 subjects were enrolled from acute care settings (14 EGZB; 11 Charité-ITS) and 195 subjects were recruited across 18 different nursing homes.

Nr	Participating ward	Number of patients (n)
Geriatric hospitals		
1	EGZB	14
2	Charité intern ITS	11
Nursing homes		
1	NH-01	11
2	NH-02	19
3	NH-03	5
4	NH-04	19
5	NH-05	17
6	NH-06	10
7	NH-07	6
8	NH-08	9
9	NH-09	7
10	NH-10	19
11	NH-11	4
12	NH-12	25
13	NH-13	8
14	NH-14	7
15	NH-15	3
16	NH-16	3
17	NH-17	13
18	NH-18	10

3.1 Recruitment

All study procedures will be performed at the Charité.



4 Analysis variables

According to study protocol version 1.1, 15th June 2022, the following table presents the collected variables (first column). In total, eight study visits are planned. After inclusion, residents will be followed-up for 14 days.

Table 3: Study schedule for individual participants.

	Days														
	Enrollment	**Allocation**	**Post-allocation**												**Close-out**
Timepoint	**-5 to 0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Formal requirements and allocation																
Eligibility screening	x															
Informed consent	x															
Randomization and allocation		x														
Participant characteristics																
Demographic variables (e.g. age, sex, care level)		x														
Relevant medical diseases		x														
Relevant medications		x														
Physical function (Barthel-Index)		x														
Cognitive status (MMSE)		x														
Incontinence characteristics		x														
Clinical skin assessment																
Gent Global IAD categorization (GLOBIAD)		x		x		x		x		x		x		x		x
Erythema (visual inspection)		x		x		x		x		x		x		x		x
Erythema (instrumental measurement)		x		x		x		x		x		x		x		x
Erosion		x		x		x		x		x		x		x		x
Maceration		x		x		x		x		x		x		x		x
IAD-related pain (NRS or PAINAD-G)		x		x		x		x		x		x		x		x
IAD-related itch		x		x		x		x		x		x		x		x
Patient satisfaction (NRS)		x		x		x		x		x		x		x		x
(Serious) Adverse Events or Incidents		x		x		x		x		x		x		x		x
Interventions and study-related procedures																
Study arm 1: Conduction of the standardized skin cleansing regime and application of the film-forming skin protectant		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Study arm 2: Conduction of the standardized skin cleansing regime and application of the hydrophobic skin protectant		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Study arm 3: Conduction of the standardized skin cleansing regime, no additional skin protectant		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Other																
Skin care diary completed by nurses		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

4.1 Demography and baseline characteristics

Demographic information (e. g. age, sex, care level), incontinence type according to medical records, medical information (e. g. relevant main medical diagnoses and relevant regular medication) and further care specific data is collected for all participants.

Characteristic	eCRF table	Variable name	Type	Scale	Comment/Analysis
Patient-ID		mnpaid			
Visit Number		mnpvisno			
	mnppid_random				Randomization information (strata)
arm		rd_0050	cat	1-A 2-B 3-C	Blinded (label permutated)
	mnppid_visit				Visit information
Visit performed?		visit_0011	Cat.		
Date of visit		visit_0012	Date		
Reason for no visit		visit_0013	Char.		
Setting		sc_0020	Cat.	1-Nursing home (NH) 2-Geriatric Hospital (GH)	Important: mnppid_visit; not mnppid_screening! =>rename setting_ sc_0020
	mnppid_completion				
Date of study termination		sc_0010	Date		For "time under study" Take diff(sc_0010,visit_0012==Day0)
Did the subject complete the study regularly?		sc_0021	cat	1-Yes, completion of end of study visit on Day 14 2-Yes, but before end of study visit on Day 14 0-No	Reasons for 0 might be withdrawal before randomization or screening failure
Reasons for early termination		Sc_0031 to Sc_0038			Consider sc_003x_txt Except for 0031,0032,0037

Characteristic	eCRF table	Variable name	Type	Scale	Comment/Analysis
	mnppid_demo				Demography & Medical Data
A Demography					
Age		dm_0020	Cont.	years	Mean (sd)
Sex		dm_0030	cat	1-male 2-female	n (%)
Body height		dm_0041	Cont.	cm	Mean (sd)
Body weight		dm_0051	Cont.	kg	Mean (sd)
BMI		dm_0060	cont	Score	Mean (sd)
Care level		dm_0070	cat	0-none 1-1 2-2 3-3 4-4 5-5 -1-Unknown	n (%)
Smoking status		dm_0080	cat	1-Smoker 2-Non-Smoker -1-Unknown	n (%)
Skin type		dm_0090	cat	1-I 2-II 3-III 4-IV 5-V 6-VI	n (%)
B Medical Data					
Relevant medical diagnoses (ICD 11)			multi		Multiple answers possible
None		dm_0101	cat	0-no 1-yes	n (%)
Hypertension		dm_0102	cat	0-no 1-yes	n (%)
Dementia		dm_0103	cat	0-no 1-yes	n (%)
Renal failure		dm_0104	cat	0-no 1-yes	n (%)
Diabetes mellitus		dm_0105	cat	0-no 1-yes	n (%)
Heart arrhythmia		dm_0106	cat	0-no 1-yes	n (%)
Unknown		dm_0107	cat	0-no 1-yes	n (%)
Relevant medications			multi		Multiple answers possible

Characteristic	eCRF table	Variable name	Type	Scale	Comment/Analysis
None		dm_0111	cat	0-no 1-yes	n (%)
Antithrombotics		dm_0112	cat	0-no 1-yes	n (%)
Beta-adrenoreceptor antagonists		dm_0113	cat	0-no 1-yes	n (%)
Diuretics		dm_0114	cat	0-no 1-yes	n (%)
Medication influencing the renin angiotensin		dm_0115	cat	0-no 1-yes	n (%)
Psychoanaleptics		dm_0116	cat	0-no 1-yes	n (%)
Antibiotics		dm_0117	cat	0-no 1-yes	n (%)
Unknown		dm_0118	cat	0-no 1-yes	n (%)
Diarrhoea		dm_0120	cat	1-Yes 0-No -1-Unknown	n (%)
Urinary tract infection		dm_0130	cat	1-Yes 0-No -1-Unknown	n (%)

4.2 Outcome variables

Because of the exploratory nature of the trial and according to methodological guidance for exploratory trials, a distinction between primary and secondary endpoints is not made [23]. The presence of IAD is, however, with consideration of the study protocol considered as main outcome variable, i.e. primary outcome.

Variables marked with (day0) will considered as baseline data. All outcome variables are measured in eight study visits in total (one baseline visit [Day0] and seven follow-up visits [Day2, Day4, …, Day14]).

Characteristic	eCRF table	Variable name	Type	Scale	Comment/Analysis
IAD incidence	mnppid_skin				**Main outcome** Measured via occurrence of IAD at given visit (skin_0011)
IAD present?		skin_0011	cat	0-no 1-yes	n (%)
Location front		skin_0015	cat	0-no 1-yes	n (%)
Location back		skin_0016	cat	0-no 1-yes	n (%)
GLOBIAD category (front)		skin_0012	cat	1-1A 2-1B 3-2A 4-2B	n (%) (check skin_0015)
GLOBIAD category (back)		skin_0017	cat	1-1A 2-1B 3-2A 4-2B	n (%) (check skin_0016)
Erythema (visual)					Multi variable
"Redness?"		skin_0021		0-None 1-Pink 2-Red/bright red	main focus if available, else build variable based on 0026, 0027a and 0028a; (highest level counts) n (%)
n.a.		skin_0023		0-no 1-yes	Check if contradicts skin_0026, 0027a and 0028a
None		skin_0026		0-no 1-yes	
Pink		skin_0027a		0-no 1-yes	
Front		skin_0027b		0-no 1-yes	n (%)
Back		skin_0027c		0-no 1-yes	n (%)
Red/bright red		skin_0028a		0-no 1-yes	
Front		skin_0028b		0-no 1-yes	n (%)
Back		skin_0028c		0-no 1-yes	n (%)
Erythema level (1)		Func_0081 (day0) func_0141	Numeric	Arbitrary units (AU) from 0 (= no erythema) to 999 (= extreme erythema)	Mean (sd) check func_0082 func_0142, func_0143
Erythema level (2)		Func_0083 (day0) func_0144	Numeric	Arbitrary units (AU) from 0 (= no erythema) to 999 (= extreme erythema)	Mean (sd) check func_0084

Characteristic	eCRF table	Variable name	Type	Scale	Comment/Analysis
					func_0145, func_0146
Erythema level (total)			Numeric	Arbitrary units (AU) from 0 (= no erythema) to 999 (= extreme erythema)	Mean (sd) of (Erythema level 1 + Erythema level 2)/2
Erosion					
"Erosion present?"		skin_0041		0-no 1-yes	n (%)
Front		skin_0044		0-no 1-yes	n (%)
Back		skin_0045		0-no 1-yes	n (%)
Maceration					
"Maceration present?"		skin_0051		0-no 1-yes	n (%)
Front		skin_0054		0-no 1-yes	n (%)
Back		skin_0055		0-no 1-yes	n (%)
Local intolerances					
Have any local intolerances occurred since the last visit?		skin_0061		0-no 1-yes	n (%)
current condition		skin_0062		1-Homogeneous redness with scattered papules 2- Homogeneous redness and homogeneous infiltration 3- Homogeneous redness and infiltration with vesicles 4- Homogeneous redness and infiltration with coalescing vesicles	n (%)

Functional assessments					
Characteristic	**eCRF table**	**Variable name**	**Type**	**Scale**	**Comment/Analysis**
MMSE	mnppid_assessments (day0) mnppid_assessments1 (else)				Relevant for dementia and IAD related pain
MMSE-Score	mnppid_assessments	Func_0021	Numeric	Score; Range 0-30	Mean (sd)

Functional assessments					
Characteristic	**eCRF table**	**Variable name**	**Type**	**Scale**	**Comment/Analysis**
MMSE Score unknown	mnppid_assessments	Func_0022	cat	0-no 1-yes	
Has the subject a MMSE Score of 24 or higher?	mnppid_assessments1	Func_0090			Check func_0021
Cognitive Ability	mnppid_assessments	Func_0030		1-≥ 24 (Normal cognition; no dementia) 2-19 to 23 (Mild dementia) 3-10 to 18 (Moderate dementia) 4-9 and lower (Severe dementia)	N (%) Result of func_0021
Barthel Index Physical function	mnppid_assessments	Func_0041	Numeric	Score; Range 0-100	Mean (sd)
Barthel Index unknown	mnppid_assessments (day0)	Func_0042	cat	0-no 1-yes	
IAD related pain					Choice of Score depending on MMSE
IAD present?	mnppid_assessments (day0)	func_0057	cat	0-no 1-yes	Compare with skin_0011
NRS (numeric rating scale)	mnppid_assessments (day0) mnppid_assessments1 (else)	Func_0052 (day0) func_0101	Numeric	0 - 10 [numeric]	Mean (sd) if (MMSE Score ≥ 24) (check func_0051) (check func_0102 and 0103)
PAINAD-G	mnppid_assessments (day0) mnppid_assessments1 (else)	Func_0054 (day0) func_0111	Numeric	0 - 10 [numeric]	Mean (sd) if (MMSE Score < 24) (check func_0053) (check func_0112 and 0113)
No assessment	mnppid_assessments (day0)	Func_0055	cat	0-no 1-yes	
IAD related itch					
IAD-related itch reported by patient?	mnppid_assessments (day0) mnppid_assessments1 (else)	Func_0061 (day0) func_0121	cat	-2-No assessment -1- N.A. (no IAD present) 0-No 1-Yes	Func_0062 and func_0122 for missing analysis

Functional assessments					
Characteristic	**eCRF table**	**Variable name**	**Type**	**Scale**	**Comment/Analysis**
Patient satisfaction (of incontinence treatment)	mnppid_assessments (day0) mnppid_assessments1 (else)	Func_0071 (day0) func_0131	Numeric	0 - 10 [numeric]	Mean (sd) if (MMSE Score ≥ 24) (check func_0053) NRS from 0 (= dissatisfied) to 10 (= very satisfied) (check func_0072 for missings) and func_0132,func_0133)

4.3 Secondary variables

The main clinical outcome is IAD incidence. All other outcome variables are considered secondary.

4.4 Efficacy

The main efficacy variable is the IAD cumulative incidence measured by IAD presence on each visit day (Day0, Day2, …, Day14). Secondary efficacy variables are Erythema and Maceration level, IAD itch and pain level and patient satisfaction.

- IAD-related itch and pain level (numeric rating scale) are measured at each visit day (Day0, Day2, …, Day14) if IAD is present and if MMSE ≥ 24.
- IAD itch and pain level (PAINAD-G) are measured at each visit day (Day0, Day2, …, Day14) if IAD is present and if MMSE < 24.
- Patient satisfaction is measured at each visit day (Day0, Day2, …, Day14) if MMSE ≥ 24
- Erythema and Maceration level are measured at each visit day (Day0, Day2, …, Day14).

4.4.1 Safety/Tolerability

Events are defined according to the definition of the EU regulation 2017/745 Medical Device Regulation (MDR) Article 2 and will be checked regularly.

Adverse events

- Untoward medical occurrence, e.g. allergic reaction
- Unintended disease or injury
- Untoward clinical signs, e.g.: abnormal laboratory finding

Incidents

- any malfunction or deterioration in the characteristics or performance of the skin protectants

Serious adverse events / Serious incidents that (in-)directly lead to

- Death
- Serious deterioration in the health

4.4.2 Quality of life

There is no specific questionnaire for quality of life assessment.

4.4.3 Feasibility and adherence

Feasibility and adherence relevant outcomes are evaluated by analysing the available diaries for the study. Due to the nature of the diaries, they will be evaluated separately by an unblinded person of the study team to ensure the blindedness of the statistician for further analyses.

Characteristic		Type	Scale	Comment/Analysis
Feasibility	Diary			
-	-	-	-	Assessment not possible
Adherence	Diary			
Percentage of completely/ correctly documented days:		Numeric	xx [%]	Count diary_00x1 per patient *x…# of day* *(opt.: divide by days under study)* Each diary day includes several variables (e.g. count of urinary incontinence episodes, count of stool incontinence episodes, change of incontinence material, product application, etc.). A day is defined as follows: • Correctly documented: All fields are fully completed (100% documented). • Partially correct: One or more fields are missing. • Not filled: Only the date is recorded and all other entries are missing. Note: A "missing" entry indicates that data was not provided, while a deliberate zero indicates that the event did not occur.
Number of product applications		Numeric	Xx [quantity]	Summarize diary_00x6y per patient, per day and week *x…# of day* *y…letter of application on day x*

5 Handling of missing values and outliers

5.1 Missing values

In all analyses, missing values on either the outcome measures or on the covariates will be handled by using multiple imputation by chained equation (MICE) with *m* = 30 imputed datasets if MAR or MCAR assumption holds. To evaluate whether individual missings are MAR, MCAR or MNAR we will use information on reasons of missings or drop out (e.g. if patients drop out due to worsening of health status or not). In case of death, no imputation will be implemented for the time afterwards.

6 Sample size

Due to the exploratory nature of the trial, a formal sample size calculation is not applicable [23]. The trial has two subgroup strata (I) sex (male/female); (II) condition of the skin (no IAD vs. IAD Category 1A) and three treatment arms. Based on these conditions and following the recommendations for exploratory trials [36], a sample size of n = 60 participants per treatment group is considered feasible and sufficient to describe group differences. In order to compensate a possible loss-to-follow-up, n = 70 patients per group will be included.

7 Statistical analyses / methods

For all analyses, appropriate descriptive statistics (mean, standard deviation, median, interquartile range, absolute and relative frequencies) depending on the scale and distribution of the outcome variable for each time point will be presented. For relative frequencies of outcome variables, their cumulative incidences will be reported as well. Sensitivity analyses include per protocol analyses and complete case analyses in the ITT (without imputation).

7.1 Demography and baseline characteristics

Demography and baseline characteristics will be presented descriptively without any comparisons. Depending on the distribution either mean or median will be reported with standard deviation or interquartile range respectively.

7.2 Analyses of endpoints

Because of the exploratory nature of the trial and according to methodological guidance for exploratory trials, a distinction between primary and secondary endpoints is not made [23]. Because the main aim is to prevent IAD, IAD incidence is likely to be considered as a primary outcome in a possible subsequent confirmatory trial and is therefore considered as primary efficacy variable.

For all outcomes, total group differences are reported by the corresponding effect size based on the statistical models as outlines below and corresponding 95% confidence intervals. Relevant timepoints will be Day 6 and Day14. Day0 reports will be presented as is.

The relevant blinded group comparisons are: A vs. B; A vs. C; B vs. C.

For cumulative incidence rates of IAD, Kaplan-Meier Curves will be presented with time ranging from inclusion to IAD onset, i.e. the first occurrence of IAD 2A or 2B. Censoring occurs if patients withdraw from the study before the onset of an IAD or if the study is terminated before IAD onset. Mixed effects Cox regression model (shared frailty model) will be carried out for group comparisons of incidence rates. The latter includes group allocation, sex, setting (nursery home, geriatric hospital ward) and time (continuous) as fixed effects and random intercepts for the ward and the patients.
The resulting Hazard ratios for IAD will be presented. Potential non-linear time effects will be explored and modelled using fractional polynomials or splines.

Group differences for categorical, dichotomous responses are calculated by estimating group effects from either generalized linear mixed-effects models (binary logistic) - including particular baseline status (maceration, IAD-related itch), group allocation, sex, setting and time as fixed effects and random intercepts per ward and patients - or nonparametric analysis of longitudinal data depending on the distribution of the data. For the Erosion model, no baseline adjustment is considered due to its presence is an exclusion criterion.

List:

- Erosion (no/ yes)
- Maceration (no/ yes)
- IAD related itch (no/ yes) [only measured if IAD present]
- IAD-related pain (no/yes) [only measured if IAD present]

Group differences for numerical, ordinal responses are calculated by estimating group effects from either cumulative link mixed-effects (ordinal) - adjusted for baseline status, group allocation, sex, setting and time as fixed effects and random intercept per ward-ID and patient as random effects - or nonparametric analysis of longitudinal data depending on the distribution of the data.

In case of non-occurrence of one category, the model will reduce to a generalized linear mixed-effects models (binary logistic) as stated above.

List:

- Erythema (none/pink/red or bright red)

Group differences for numeric, interval scaled responses are calculated by estimating group effects from either linear mixed-effects models - adjusted for baseline status, group allocation, sex, setting and time as fixed effects and random intercept per ward and patient as random effects - or nonparametric analysis of longitudinal data depending on the distribution of the data.

List:

- Erythema (total) level (in arbitrary units (AU) from 0 to 999)
- IAD related pain (numeric rating scale from 0 to 10) [for IAD present]
- Patient satisfaction (numeric rating scale from 0 to 10) [both: for MMSE ≥ 24 and above]

In case of nonlinear relationship, nonlinear mixed-effects models will be considered. The check will occur visually by scatterplots.

The distribution of outcome variables will be checked by raincloud plots (boxplot + histogram).

No adjustment for multiple comparisons will be made and results are bound to be seen exploratory.

7.2.1 Efficacy

The endpoints will be compared exploratory between the three groups. No confirmatory statistical tests will be conducted. Primary efficacy analyses will be carried out in an ITT framework using multiple imputed datasets in case of missing values (under the assumption of MCAR or MAR).

7.2.2 Safety/Tolerability

AEs, SAEs, incidents and serious incidents will be -if any occurred- listed per patient and for the total trial.

The safety analysis based on the safety analysis set (according to the patients' received treatment) includes calculation of frequencies and incidence rates as well as incidence rate ratios and corresponding 95% confidence intervals of adverse and serious adverse events using poisson regression or negative binomial regression models depending on the distribution of the variables.

Results of safety analysis will be interpreted and discussed thoroughly also for minor group differences, since statistically significance is not of importance here.

7.2.3 Quality of life

Quality of life is assumed to be linked with patient satisfaction and the interview part. There is no specific separate questionnaire.

7.3 Planned subgroup analyses

Differential treatment effects will be analyzed by including interaction terms for subgroups by intervention group. Prespecified subgroups include sex (male/female) and patients with and without IAD 1A status at baseline. For the subgroup consisting of no initial IAD, a second time-to-event analysis will be realized, using the first occurrence of any IAD category as event and thus including 1A and 1B. Additionally, location (front/back) of IAD and Erosion will be considered for subgroup analyses as well. Parallel to interaction effects estimated marginal treatment effects of the subgroups and 95% CI will be reported.

7.4 Interim analyses

No interim analyses are planned in this study.

8 Software

We will use the data management software REDCap for data handling and storage, as well as the open source software R for all analysis steps in version 4.2.0 or greater.

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10 Appendix

10.1 Program code

The statistical code for analysis of the endpoints will be made available on drks.de

10.2 Exemplary table layouts

Table 1: PID - Demographics

Characteristic	**Overall** N =	**Group A**, N =	**Group B**, N =	**Group C**, N =
Age				
Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Median [IQR]	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]	x.xx [x.xx; x.xx]
(Minimum,Maximum)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)
Sex, n (%)				
Female	x (pp.p)	x (pp.p)	x (pp.p)	x (pp.p)
Ward setting, n (%)				
Geriatric hospital	x (pp.p)	x (pp.p)	x (pp.p)	x (pp.p)
Nursing ward	x (pp.p)	x (pp.p)	x (pp.p)	x (pp.p)

Table 2: PID – IAD incidence characteristics: Hazard Ratios

Predictors	**Hazard Ratio**	**95% CI**
Study arm		
A	-	-
B	x.xx	x.xx to x.xx
C	x.xx	x.xx to x.xx
Sex		
Female	-	-
Male	x.xx	x.xx to x.xx

Table 3: PID – Secondary outcome characteristics

Outcome	Contrast	Estimate	Effect size	95% CI
Maceration				
	A vs. B	x.xx	x.xx [a]	x.xx to x.xx
	A vs. C	x.xx	x.xx [a]	x.xx to x.xx
	B vs. C	x.xx	x.xx [a]	x.xx to x.xx
Erythema level				
	A vs. B	x.xx	x.xx [b]	x.xx to x.xx
	A vs. C	x.xx	x.xx [b]	x.xx to x.xx
	B vs. C	x.xx	x.xx [b]	x.xx to x.xx

a) Odds Ratio; b) Cohen's d