A protocol for a controlled, phase II, multi-arm, parallel-group, superiority, six-month trial comparing the effectiveness of far-UVC (222 nm) in two experimental arms against standard care in preventing viral and bacterial infections in long-term care facilities

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Title

A protocol for a controlled, phase II, multi-arm, parallel-group, superiority, six-month trial comparing the effectiveness of far-UVC (222 nm) in two experimental arms against standard care in preventing viral and bacterial infections in long-term care facilities

Names protocol contributors

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Trial registration

The trial is not registered at ClinicalTrials.gov (phase II trial) but was published at the University of Southern Denmark Research Portal (Pure) before the intervention started.

Protocol version

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In the case of an amendment, we will describe the primary reason for the amendment and the date of revision.

Funding

Mette Assenholm Kristensen (MAK), Emilie Hage Mogensen (EHM), and Christian Kanstrup Holm (CKH) receive salaries from UV Medico A/S, the funder of the study. The specific roles of these authors are articulated in the “Authors’ contributors” section. The funder provides support in the form of salaries and far-UVC lamps, besides financing the cost of receiving data from national registers (The Danish Health Data Authority). However, they will not play any role in data collection and analysis.

Abstract

Background

Elderly residents in long-term care (LTC) facilities are highly susceptible to infections, often leading to hospitalizations and placing significant strain on the healthcare sector. The COVID-19 pandemic underscored the importance of airborne pathogen transmission and highlighted the necessity for targeted interventions that require minimal healthcare personnel resources to protect elderly populations. Far-UVC light has emerged as a promising technology offering both germicidal efficacy and safety for human exposure, although its clinical impact remains sparsely studied. This study aims to evaluate the effectiveness of far-UVC (222 nm) in mitigating hospitalizations due to viral and bacterial infections among LTC residents.

Methods

The study is designed as a controlled, phase II, multi-arm, parallel-group, superiority, 6-month trial conducted in LTC facilities in Denmark. The LTC facilities will receive either far-UVC lamps or standard care with an allocation ratio of 1:1:10. One of the LTC facilities will be equipped with far-UVC lamps (experimental arm one) in common areas, while another will be equipped with far-UVC lamps (experimental arm two) in common areas and residents' apartments. We plan to include 12 public LTC facilities in Vejle with 542 residents. Outcome data will be obtained from nationally validated health registers. The primary outcome is LTC facility-acquired infections (lower respiratory tract infections, urinary tract infections, and bloodstream infections), which cause hospitalization. The key secondary outcome is prescribed antibiotics at LTC facilities, alongside monitoring all-cause mortality, cause-specific mortality (infection), and adverse events.

Discussion

This trial aims to determine the clinical impact of far-UVC technology in LTC facilities. In the case of sufficiently promising effectiveness, a large-scale cluster randomized phase III will be carried out.

Introduction

Background and rationale

Elderly residents in long-term care (LTC) facilities are particularly vulnerable to infections due to age-related changes in their immune systems, small living quarters, and shared caregivers. The most common infections are urinary tract infections and pneumonia, which increase the risk of invasive diseases and hospitalizations [1]. Outbreaks of infectious diseases are also common in LTC facilities, affecting a large number of residents [2]. Once introduced, respiratory tract pathogens, gastrointestinal pathogens, or pathogens leading to skin and soft-tissue infections often disseminate rapidly among residents and staff [2]. Depending on the infectious agent, they may spread through more than one transmission route (e.g., contact or airborne transmission). The COVID-19 pandemic broadened our understanding of the transmission of pathogens through air, and recent studies have suggested that most respiratory viruses are primarily transmitted by small and large aerosols (microdroplets) [3], defined as infectious respiratory particles [4]. Therefore, preventive measures related to buildings, such as ventilation, air filtration, and air disinfection, have been recognized as increasingly important tools in infection control [3].

Ultraviolet C (UVC) light is widely recognized for its germicidal properties and has traditionally been employed through low-pressure mercury lamps that emit UV light at 254 nm. While germicidal effectiveness is well known, its use is restricted to unoccupied spaces or to upper-room germicidal irradiation due to its harmful effects on human skin and eyes [5]. Meanwhile, a new technology, "far-UVC" (200–230 nm), has gained attention for controlling disease transmission by inactivating microorganisms both in air and on surfaces. This technology uses filtered krypton chloride light sources that emit light at 222 nm, with the filter blocking residual emissions outside the 222 nm peak [6]. Far-UVC irradiation has been shown to inactivate bacteria, viruses, and fungi [7–9], including pathogens such as influenza viruses [10] and SARS-CoV2 [11], which pose significant global health risks, particularly to the elderly [12,13]. Beyond its germicidal capabilities, far-UVC has been demonstrated to be safe for skin [14–16] and eyes [17,18] when applied within regulatory limits. These are attributed to the high absorption of far-UVC by proteins [19], preventing irradiation from penetrating beyond the stratum corneum, the outermost layer of dead cells on the skin, and the outermost epithelial layer, which is covered by a protein-rich tear film that protects the cornea [14]. Therefore, installing far-UVC in LTC facilities can lower the level of pathogens in air and on surfaces, thereby reducing the risk of disease transmission and hospitalizations among the vulnerable elderly. This study protocol is written according to the guideline for protocols of clinical trials, the "SPIRIT" guideline [20].

Objectives

The clinical impact of far-UVC on infectious diseases remains sparsely studied. Thus, this study aims to determine the effectiveness of far-UVC (222 nm) in reducing hospitalizations due to viral and bacterial infections, compared to standard care, among residents in LTC facilities. The primary objective is to determine the effectiveness of far-UVC lamps in common areas or common areas plus residents' apartments, relative to standard care, in reducing hospitalizations caused by LTC facility-acquired lower respiratory tract infections, urinary tract infections, and bloodstream infections. The primary hypothesis is that the use of far-UVC lamps in both common areas and residents' apartments will reduce infection-related hospitalizations compared to standard care. The secondary

hypothesis is that the use of far-UVC lamps in common areas will reduce infection-related hospitalizations compared to standard care.

If sufficiently promising effectiveness is demonstrated, a large-scale randomized phase III trial will be conducted.

Trial design

This experimental study will be designed as a controlled, phase II, multi-arm, parallel-group, superiority, six-month trial. Two experimental arms and one control arm will be compared, with an allocation ratio of 1:1:10. One of the LTC facilities will be equipped with far-UVC lamps (experimental arm one) in common areas and another will be equipped with far-UVC lamps (experimental arm two) in common areas and residents' apartments. The remaining 10 LTC facilities will receive standard care and serve as the control arm. We plan to include 542 residents in this trial. Four of the 16 public facilities in Vejle Municipality were excluded following the listed criteria (see section "Eligibility criteria").

Methods: Participants, interventions, and outcomes

Study setting

The study will be conducted in public LTC facilities in Vejle Municipality, located in the southern part of Jutland, Denmark. Collaborative partners include the municipal leadership of the Department of Health in Vejle; researchers from the Department of Clinical Microbiology, Lillebaelt Hospital, Vejle, Denmark; researchers from the Department of Biomedicine, Aarhus University, Aarhus, Denmark; and those from UV Medico A/S, Aarhus, Denmark. In the Vejle Municipality, 3.4% of individuals aged 67 and above reside in one of the 20 LTC facilities [21]. In Denmark, elderly individuals typically move into LTC facilities only when their needs cannot be met through home care. Therefore, frailty and dementia are highly prevalent in LTC facilities. Most LTC facilities in Denmark are public [22], and in Vejle Municipality, 16 out of 20 are public. The prevalence of infections in LTC facilities in Denmark is 5.7% [23].
All residents of LTC facilities in Vejle have private apartments with bathrooms and a kitchenette. The indoor environment is maintained with humidity levels ranging from 25% to 60% and temperatures between 20℃ and 25℃. Common areas with high occupant density and activity and the residents' apartments are the focus of this phase II trial.

The infection control guidelines in Danish LTC facilities follow a multimodal prevention strategy aimed at enhancing host defenses in the elderly, preventing the transmission of pathogens, and treating infections, with a primary focus on standard precautions. Source isolation is not practiced in Danish LTC facilities; however, additional (transmission-based) precautions, such as the use of personal protective equipment, are recommended in extraordinary cases such as when COVID-19 or methicillin-resistant *Staphylococcus aureus* is diagnosed among residents [24]. Adherence to infection control interventions, such as physical distancing, covering coughs, and hand hygiene, is generally low among residents due to their fragility.

In Denmark, all citizens with permanent residences are assigned a unique 10-digit Central Personal Register (CPR) number, which is used across all Danish public registries and allows for the linkage of individual data [25,26].

Eligibility criteria

This study will include public LTC facilities in Vejle Municipality and the residents living in these facilities. The following LTC facilities will be excluded: 1) non-standardized buildings (building type or layout); 2) facilities with an increased risk of infections, such as those sharing common areas with kindergartens; and 3) facilities for individuals with dementia. In addition, we will exclude all residents receiving respite care or living in assisted-living facilities. New individuals moving into one of the participating LTC facilities will be screened for eligibility shortly after their arrival.

Intervention description

Eligible LTC facilities will be assigned to receive either far-UVC lamps (experimental arm one or experimental arm two) or standard care. The active intervention in experimental arm one will be the use of far-UVC lamps in common areas (dining hall and living room) and that in experimental arm two will be the use of far-UVC lamps in common areas and residents' apartments. The far-UVC lamp that will be used in this study is a UV222™ lamp (UV Medico A/S, Denmark), which contains a krypton chloride excimer light source emitting filtered far-UVC irradiance at 222 nm and 60° angle. The optical filter (Care 222®, Ushio Inc., Japan) attenuates residual wavelength emission outside the 222-nm peak. The output is 115 mW, with a far-UVC irradiance of 13.7 $\mu W/cm^2$ one meter from the lamp. The lamps will be configured to operate automatically in duty cycles to ensure that the threshold limit value (TLV) of 23 mJ/cm^2 for the residents and personnel, as recommended by the International Commission on Non-ionizing Radiation Protection, is not exceeded [27]. The UV222™ lamp carries a CE mark, which certifies its compliance with all European Union health and safety standards.

The lamps will be installed in the ceiling and configured by an employee from Medico A/S using UV222™ software (UV Medico A/S, Denmark). The configuration of each lamp will depend on its location within the room, the size of the room, and the time of occupancy by the residents and personnel. In general, the lamps will be configured to deliver the maximum far-UVC dose without exceeding the TLV.

To prevent co-intervention bias, we will inform the participating LTC facilities that other infection control measures during the six-month-long trial may introduce bias. To evaluate co-intervention bias, we will collect data on infection control measures that have a substantial impact on infection rates (e.g., mechanical ventilation).

Provisions for post-trial care

According to the literature [14–18], we do not expect post-trial care or ancillary interventions. However, if the treatment of adverse events related to trial procedures is required, trial sponsors and investigators will ensure that sufficient care is provided. In Denmark, which provides free access to healthcare and subsidized medication, affected participants, including employees at LTC facilities, will receive appropriate care.

Outcomes

The primary outcome is to determine the number of hospitalizations due to the selected LTC facility-acquired infections: lower respiratory tract, urinary tract, and bloodstream infections. We will identify the LTC facility-acquired infections by 1) discharge diagnosis using the International Classification of Diseases 10th Revision (ICD-10) codes or 2) antibiotics covering empirical treatment or antiviral agents for the included infection types within 48 h of hospital admission, using the Anatomical Therapeutic Chemical (ATC) code. Criterion 1 (ICD-10) or criterion 2 must be met for an infection to be classified as LTC-facility acquired.

To avoid including infections acquired before the onset of the study (e.g., in the incubation period), the first infection should occur more than seven days after the resident is included in the study. New infections will be included if identified 30 days after a previously identified infection. LTC facility-acquired infections occur in patients without recent hospital exposure. Therefore, infections in patients who were hospitalized within the last 14 days will be considered hospital acquired. Furthermore, residents with frequent hospitalizations (more than six during the study period) or prolonged hospitalizations (over two months) will be excluded due to uncertainty regarding where the infection was acquired.

The key secondary outcome is the consumption of systemic antimicrobial agents prescribed by general practitioners for residents who are not hospitalized. Furthermore, we will measure cause-specific mortality (infection) and all-cause mortality. Safety is another secondary outcome, and we will monitor adverse events for the far-UVC groups throughout the study. We will grade the severity of the adverse events according to standard definitions, if available. The limit value for ozone exposure is 0.1 ppm or 0.2 mg/m^3 according to the Danish Working Environment Authority regulations [28].

Participant timeline

The participants will remain part of the study until the end of follow-up, death, or relocation from the LTC facility. For each enrolled participant, their involvement will be measured in terms of resident days.

Recruitment

To recruit LTC facilities, we will arrange pre-study meetings with the Department of Health in Vejle Municipality and the managers of the LTC facilities. We will provide a video in Danish for the employees at the participating LTC facilities, along with pamphlets for residents and their relatives. These materials will be written in layperson terms.

The study schedule is outlined in Table 1.

Table 1: Schedule of enrolment, interventions, and assessments

	STUDY PERIOD			
	Enrolment	Intervention		Close-out
TIMEPOINT	Oct 2024	Nov-Dec 2024	Jan-Apr 2025	May 2025
ENROLMENT:				
Eligibility screen	x			
Information	x			
INTERVENTIONS:				
Far-UVC light		x	x	
ASSESSMENTS:				
Baseline variables, residents, and LTC facilities	x			
LTC facilities acquired infections*		x	x	x
All-cause mortality		x	x	x
Cause-specific mortality				
Antimicrobial consumption		x	x	x
Adverse events		x (from Dec)	x	x
Process evaluation		x	x	
*Lower respiratory tract infections, urinary tract infections, and bloodstream infections				

Methods: Assignment of interventions

Allocation

The enrolled LTC facilities will be allocated to two experimental arms and one control arm after enrollment in the LTC facilities. The two LTC facilities with the largest number of residents will be allocated to experimental arms for practical reasons and statistical power.

Implementation

After the allocation of the two experimental arms and the control arm, UV Medico A/S will provide far-UVC lamps and facilitate installation and configuration in coordination with LTC facility managers.

Methods: Data collection, management, and analysis

Plans for the assessment and collection of outcomes

To identify the study population (10-digit CPR of residents and their corresponding LTC facility), we will use the database from the Department of Authority in Vejle Municipality, which is maintained to manage grants for elderly care services. We will collect data on the study flow: for residents, we will collect data on the number and reasons for lost to follow-up (e.g., long hospitalization). To minimize participant burden, encourage participation, ensure validity, and reduce the amount of missing data, we will use data from national registers for residents' characteristics rather than relying on daily administered manual registration tools for infectious symptoms or infectious diseases.

Data on LTC facility characteristics will be collected using questionnaires and include building-related measures (mechanical/passive ventilation, air filtration, air purifiers, CO_2 measuring devices, building age, and year of last renovation) and organizational measures (staff-to-resident ratio, occupancy density, cleaning frequency, and whereabouts of the residents). The questionnaire will end with an

optional field for free-form text responses. These data will be filled in by the study coordinator of each LTC facility. To evaluate whether resident characteristics are evenly distributed between the experimental arms and control arm before the intervention, we will collect data on age, gender, comorbidities (including diabetes, chronic obstructive pulmonary disease, congestive heart failure, cancer, renal disease, coronary artery disease, and liver disease), and vaccine status (pneumococcal, influenza, and COVID) from previously validated national registers [25,29,30]. We will calculate the Charlson Comorbidity Index (CCI) score according to standardized and validated methods [31].

Data on the primary outcome variables, including those on lower respiratory tract, urinary tract, and bloodstream infections, will be obtained for each resident. We will retrieve information on prescription redemption dates for systemic antibiotic treatment from the validated Danish National Prescription Registry [32]. Data on somatic disorders (ICD codes) will be obtained from the National Patient Registry, which covers all admissions and outpatient visits to Danish hospitals (both somatic and psychiatric) [29]. For the key secondary outcome, we will obtain data on the consumption of systemic antimicrobial agents prescribed by general practitioners from the Danish National Prescription Registry [32]. For the secondary outcomes related to mortality (all-cause mortality and case-specific mortality), we will retrieve information on the date and cause of death from the Danish Civil Registration System [25] and the Danish Register of Causes of Death [33].

Data on adverse events will include measures related to ozone levels, decoloration of fixtures and furniture (dichotomous), and an optional field for free-form text responses. These data will be collected monthly during the trial, starting one month after the interventions start, through a pilot-tested questionnaire answered by the study coordinator of each LTC facility. During the trial, we will measure the ozone levels in air using a handheld measuring device from Scanion A/S “EX-1X,” which measures ozone levels from 0.02 to 0.14 ppm. Ozone levels will be measured at each included LTC facility with lamps installed, twice during the trial (Nov-Dec 2024 and Jan-Apr 2025).

Data management

We will use REDCap to manage the questionnaires and the study population during the intervention period. REDCap is a mature, secure web application designed for building and managing online surveys and databases. It meets the requirements for transaction-level logging and can store and process any personally identifiable data [34,35]. During data review and analysis, data will be stored on the Danish Health Data Authorities’ secure platform available for researchers. Review and data management will be performed by MAK and an epidemiologist from the Open Patient Data Explorative Network (OPEN). OPEN is a consultancy service for researchers, located in the Region of Southern Denmark.

Confidentiality

Residents living in the included LTC facilities will be identified using the database from the Department of Authority in Vejle Municipality. To ensure the confidentiality of the participating residents, their CPR numbers will be replaced with unique identifier numbers (pseudo-anonymized) by the Danish Health Data Authority when transferring the dataset from REDCap. The residents will then be matched with national registry data. Before using any of the collected data for publication or dissemination, the research team will ensure the anonymization and de-identification of all participating residents.

All data processing will be documented in do-files in Stata. Data and data processing files will be kept for at least five years from the date of publication in accordance with the Danish Code of Conduct for Research Integrity, Ministry of Higher Education and Science, November 2014.

Statistical Methods

We will compare the characteristics of the participating LTC facilities. Furthermore, the baseline demographic and clinical characteristics of the assigned residents will be compared in the intention-to-treat population.

Statistical methods for primary and secondary outcomes

To compare the groups, we will carry out an intention-to-treat analysis. We will calculate resident days (denominator) and the number of selected infections (numerator) to estimate the incidence rate (IR) for the intervention groups (far-UVC) and the control group (standard care). For primary and secondary outcomes (dichotomous), the incidence rate ratio (IRR) will be analyzed using Poisson's regression (or negative binomial regression if overdispersion is detected) with a corresponding 95% confidence interval. P values of less than 0.05 (two-sided) will be deemed statistically significant. Adjustments for baseline covariates or known confounders will be analyzed using multivariable regression. We will perform the adjustment for each comorbidity as a separate dichotomous covariate instead of the CCI scores, according to the recommended practice [36]. The secondary outcomes will be estimated as above; however, the numerator will be replaced with antibiotic prescriptions at the LTC facility (key secondary outcome), cause-specific mortality (infections), and all-cause mortality. In addition, the primary and key secondary outcomes will be assessed using a subgroup analysis to explore whether the estimated effectiveness varies significantly between the subcategories. The subcategory analyses will include CCI [31] and age. In the analyses, patients will be divided into three groups: none (0), mild, with CCI scores of 1–2; moderate, with CCI scores of 3–4; and severe, with CCI scores ≥5 or none (0), CCI scores of 1 and ≥2 depending on the group size. For age as well, the patients will be grouped into three categories: <75 years, 75–85 years, and >85 years. We will calculate and report missing data (number and percentage).
Adverse events will be evaluated for the far-UVC groups only. Ozone levels will be calculated as dichotome (above or below limit value for ozone level), as well adverse events related to the decoloration of fixtures and furniture (affected/not affected). Responses from the field for free-form text responses will be evaluated qualitatively by grouping themes.

All statistical analyses will be conducted using Stata version 17 (StataCorp, College Station Texas, USA) by a professional academic epidemiologist and MAK.

Oversight and Monitoring

Composition of the data monitoring committee, its role, and reporting structure

Because of the nature of the trial, we expect a low risk of intermediate errors; therefore, MAK will only visit the LTC facility one and four months after the intervention starts. Only LTC facilities allocated to an active intervention will receive a visit. During the visit, MAK will review the registration of the safety profile for far-UVC and inspect the lamps. If necessary, the research team (MAK, CKH, EHM, and Stine Yde Nielsen (SYN)) will make adjustments according to the inspection results. A data monitoring committee is not established because outcome data from both the far-UVC groups and the control group is obtained from nationally validated registers.

Plans for communicating important protocol amendments to relevant parties

For any modifications to this protocol that may impact the conduct of the study, we will make an amendment to the protocol. Modifications could arise due to factors such as patient safety, or scientific validity. Any amendment will be agreed upon by all authors of the protocol. To track the amendment history and identify the most recent protocol version, the data, and their version will be recorded in the administrative information section of the protocol, and the new version will be published in *Pure*. Any significant changes will be communicated to relevant stakeholders, such as the participating LTC facilities, and described in trial publications. Minor administrative issues that do not impact the conduct of the study will be documented in a memorandum, which will be available upon request.

Dissemination plans

The authors of the protocol (MAK, EHM, CKH, and SYN) will publish the trial results in peer-reviewed journals; even non-significant results will be published, to prevent overestimation of benefits when using far-UVC. Additionally, a preprint of the scientific paper will be made available before its publication in a peer-reviewed scientific journal. Trial results will be disseminated to the employees and residents at the participating LTC facilities as well as stakeholders at Vejle Municipality. Decisions regarding data sharing are yet to be made. If the dataset or data processing files are shared, we will select a data repository that allows us to add metadata, a unique and persistent identifier (e.g., DOI), and a license to use the dataset. This will ensure that the data can be discovered and cited by others, and the terms for reuse will be clearly defined.

Declarations

Author's contributions

MAK conceived the study design with assistance from SYN, including the study setting, outcomes, and analyses. EHM and CKH provided technical expertise on far-UVC technology, including lamp placement and configuration. MAK wrote the manuscript draft, and all authors reviewed and approved the final manuscript. MAK will lead the trial management, with monthly meetings of all authors, to ensure adherence and address any issues.

Funding

MAK, EHM, and CKH receive salaries from UV Medico A/S, the funder of the study. The specific roles of these authors are articulated in the "Authors' contributors" section. The funder provided support in the form of salaries and far-UVC lamps, as well as financing the cost of receiving data from national registers (the Danish Health Data Authority), but will not play any role in data collection and analysis.

Availability of data and materials

Access to all collected data, including the complete final trial dataset, is restricted to trial investigators at Lillebaelt Hospital (SYN, MAK) and an epidemiologist from OPEN, in accordance with the contractual agreements designed to prevent the negative consequences of sponsorship. Furthermore, Lillebaelt Hospital owns the data. Employees at the participating LTC facilities or stakeholders at Vejle Municipality do not have access to the data.

Ethics approval and consent to participate

According to the Regional Committees on Health Research Ethics for Southern Denmark (Project-ID: S-20242000 – 106), ethical approval is not required for this project. We will inform the residents and their relatives about the project, according to the General Data Protection Regulation (GDPR) art. 14. Furthermore, residents will be able to withdraw from data collection or placement of far-UVC lamps in residents' apartments at any time. We have obtained permission from the Record of Data Processing Activities in the Region of Southern Denmark (Project-ID: 24/4509) to store data.
We have provided an agreement on the transfer of data on the CPR number of residents and their respective LTC facilities from the Department of Authority in Vejle Municipality to Lillebaelt Hospital. Furthermore, we have provided a written agreement drafted by a lawyer from the Research & Innovation Organisation in the Region of Southern Denmark, signed by leaders at UV Medico A/S and Lillebaelt Hospital. This agreement outlines the interests and obligations of the parties involved.

Competing interests

EHM is a full-time employee, and CKH is a co-founder and employee at UV Medico A/S. MAK receives a salary from UV Medico A/S. There are no patents or products in development associated with this research to declare.

Project information

The research team will inform the main aspects of the trial, including an informed discussion, in writing as well as verbally to the study coordinators at the LTC facilities. A video will be used to introduce the main aspects of the trial verbally to the employees at each LTC facility. Furthermore, pamphlets will be distributed to the residents and their relatives. The employees, residents, and relatives will be able to have an informed discussion with the study coordinator of each LTC facility or, if appropriate, one from the research team (in case of unanswered questions), to ensure adequate information. Both written material and verbal information (video) will include the purpose of the trial, data collection method, risks and benefits, and competing funder interests.

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