Efficacy of Ultraviolet Germicidal Irradiation (UVGI) devices to decrease the incidence of respiratory infections in nursing homes: a cluster randomized crossover trial (RESPROTECT)

This document is a translation of the original protocol written in French.

Version n° 3.0 dated 23/09/2025

French Title	**Impact du déploiement de dispositifs d'inactivation des pathogènes de l'air par UVGI dans la lutte contre les maladies respiratoires touchant les résidents d'EHPAD**
Sponsor ID	**RIPH2_GADEA_RESPROTECT**
ID RCB	**2024-A00199-38**
SI CNRIP	**24.01457.000239**
ClinicalTrials.gov ID	**NCT06569160**

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PROTOCOL VERSIONING		
Version	**Date**	**Reason for edits**
1	29/03/2024	-
2	10/03/2025	Clarifications requested by the Scientific Advisory Board
3	23/09/2025	Edits recommended by the DSMB and approved by the SAB

SUMMARY

Title: Efficacy of Ultraviolet Germicidal Irradiation (UVGI) to decrease the incidence of respiratory infections in nursing homes: a cluster randomized crossover trial

Local title: Impact du déploiement de dispositifs d'inactivation des pathogènes de l'air par UVGI dans la lutte contre les maladies respiratoires touchant les résidents d'EHPAD

Acronym: RESPROTECT

Coordinating Investigator: Dr Cyril Cornille, Centre Hospitalier Emile Roux, Le Puy en Velay, France

Objectives

Primary objective: to compare the incidence of severe acute respiratory infections (ARIs) between periods when nursing homes (NHs) are equipped with active UVGI systems and periods when the UVGI systems are inactive.

Secondary objectives: to compare, between periods with active and inactive UVGI:

1. Incidence of ARIs of any severity;
2. Incidence of all-cause hospitalization or death;
3. Incidence of adverse events of interest (AEIs)(erythema in skin areas exposed to light and keratitis), overall and by severity grade;
4. Antibiotic consumption;
5. Presence of respiratory pathogens in air samples and on fomites;
6. Potential medico-economic benefits associated with the installation of UVGI systems

Type of study: Multicenter, open cohort, cluster randomized crossover (CRCO) quadruple-blind placebo-controlled trial.

Study setting

The study is conducted in 12 nursing homes (*Établissements d'Hébergement pour Personnes Âgées Dépendantes*, EHPAD) located in the Haute-Loire department, France.

Center eligibility criteria

Inclusion criteria:

Nursing homes:

- Having a system in place for monitoring cases of upper and lower respiratory infections among their residents.
- Agreeing to take part in the study
- Undertaking to comply with the protocol
- Accepting the installation of UVGI devices
- Undertaking to informing all residents and, where applicable, their legal representatives.

Exclusion criteria:

ENHs:

- Already equipped with another air treatment system in shared living spaces
- Declining to install UVGI devices in all rooms deemed necessary to be equipped by the coordinating investigator

- Having planned major structural changes (e.g., renovation, extension, closure, or functional requalification) during the study period that could affect the study population and/or interfere with the UVGI devices.

Individual eligibility criteria

Inclusion criteria:

All residents present for at least one day in a participating nursing home during either of the two predefined study periods are eligible. The study periods are:

- Period 1: October 1, 2024 – April 30, 2025
- Period 2: October 1, 2025 – April 30, 2026

Exclusion criteria :

Residents of participating centers are excluded if, at any time between the start of the study and the analysis of results, they or their legal representatives express the wish that their personal data not be used for the study.

Randomization

The centers included will be randomized into two arms, A and B, in a 1:1 ratio, using a centralized, computerized system.

Informed consent

This is an opt-out study. All residents of participating nursing homes receive an information notice written in accessible language, detailing the study's objectives, methodology, expected benefits, and potential constraints. The notice is also distributed to their relatives and, where applicable, their legal representatives. The notice explicitly informs residents and their representatives of their right to object, at any time, to the use of their personal data for research purposes. No data is collected for any resident who, or whose representative, expresses opposition to participation. If an opt-out request is made after data collection has already begun, all previously collected personal data is permanently deleted.

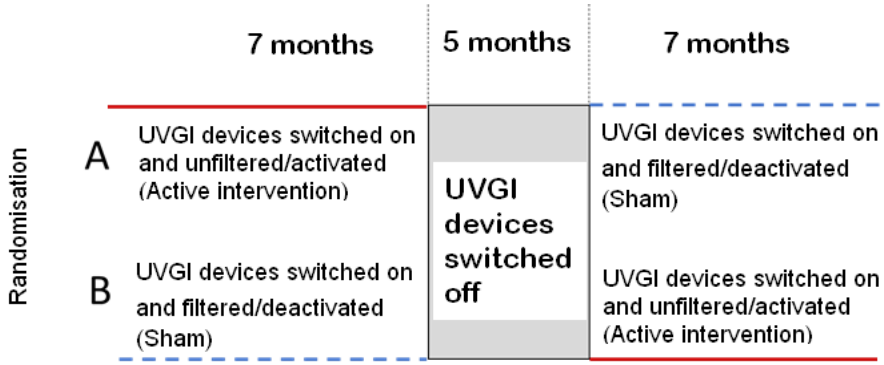
Intervention

In all the Nursing Homes included, UVGI devices will be installed and commissioned at the start of the study. These UVGI devices can be deactivated by installing an invisible internal filter. The inactivation filters will be installed by a technical team independent of the investigation team. Inactivation will therefore be carried out blind to the care givers and the investigation team.

The centers included will be randomized into two arms:

- In arm A: the UVGI device will be left active during period 1, and filtered/deactivated during period 2.
- In arm B: the UVGI device will be filtered/deactivated during period 1 and left active during period 2.

The two periods will last 7 months each, and will take place two years in a row on the same dates (October 1 to April 30). They will be separated by a 5-month wash-out period (May 1 to September 30), during which all UVGI devices will be switched off in both arms.



Endpoints

Primary endpoint:

Incidence of severe* symptomatic acute upper and lower respiratory infections**

* severe = leading to oxygen therapy, hospitalization or death

** sinusitis, otitis media, nasopharyngitis, angina, tracheitis, bronchitis, pneumonia, pulmonary abscesses and COPD exacerbations. Documented symptomatic infections with SARS-Cov-2, influenza virus, or respiratory syncytial virus, will be considered by default as respiratory infections, even if extra-respiratory symptoms predominate.

Secondary endpoints:

1. Incidence of ARIs of any severity;
2. Incidence of all-cause hospitalization or death;
3. Incidence of adverse events of interest (AEIs)(erythema in skin areas exposed to light and keratitis), overall and by severity grade;
4. Antibiotic consumption;
5. Presence of respiratory pathogens in air samples and on fomites;
6. Potential medico-economic benefits associated with the installation of UVGI systems

Main statistical analysis

The main comparison will focus on the incidence of first severe ARIs between follow-up periods with unfiltered and filtered UV devices. The numerator will be the number of people who experienced at least one acute respiratory infection during a given period. The denominator will be the cumulative follow-up time of participants up to the first acute respiratory infection or exit from the period. The result will be expressed as an incidence ratio with a 95% confidence interval.

In the first instance, the analysis will be carried out at the individual level. A generalized linear mixed model will be used, with a Poisson distribution or a negative binomial distribution in the case of overdispersion, a logarithmic link function and an *offset* term for the number of patient-years. The model will take into account intervention and period fixed effects and random effects at cluster, cluster-period, cluster-individual and individual levels. The correlation structure will be of the exchangeable block type. In the second instance, if the model does not converge, the analysis will be carried out at cluster level.

Sensitivity analyses will be carried out:

- using as endpoint: cumulative incidence of severe acute respiratory infections with the total number of severe acute respiratory infections in the numerator and the cumulative follow-up time to exit from the period in the denominator.

- by adjusting the model on the following variables: age, gender, and GIR index.

Schedule

- Start date: October 1st, 2024
- Follow-up for each period: 7 months + 30 additional days to monitor the evolution of ongoing ARI, hospitalization and AEI[1] at the end of the first 7 months
- End of study: May 31, 2026
- Total study duration: 20 months

LIST OF ABBREVIATIONS

ARI: Acute Respiratory Infections

AEI: adverse event of interest

CFU: Colony-Forming Unit

eCRF: electronic Case Report Form

CTCAE: Common Terminology Criteria for Adverse Events

CTU: Clinical Trial Unit

NH: Nursing homes (in French: **EHPAD**: *Établissement d'hébergement pour personnes âgées dépendantes*)

GIR score : *Groupe Iso-Ressources* score (French dependency score)

UVGI: Ultraviolet Germicidal Irradiation

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1. GENERAL INFORMATION

1.1. Research title

Efficacy of Ultraviolet Germicidal Irradiation (UVGI) devices to decrease the incidence of respiratory infections in nursing homes: a cluster randomized crossover trial (RESPROTECT)

1.2. Sponsor

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1.3. Study team

Coordinating investigator: Dr Cyril CORNILLE, Department of General Medicine, C.H. Emile Roux, 43000 Le Puy-en-Velay, France, Tel: +33 (0)4.71.04.35.00

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Study centers :

Twelve nursing homes (In French: *Etablissements d'hébergement pour personnes âgées dépendantes* - EHPAD), are taking part in the study:

- EHPAD public, Langeac
- EHPAD public Hôpital de proximité "Pays de Craponne", Craponne sur Arzon
- EHPAD public "les Patios du Velay", Le Puy en Velay
- EHPAD privé "Résidence Sigolène", Sainte Sigolène
- EHPAD public "L'Age d'Or", Monistrol sur Loire

- EHPAD public "Saint Jacques", Saugues
- EHPAD privé "Nazareth", Le Puy en Velay
- EHPAD privé "Paradis Fondation", Espaly Saint Marcel
- EHPAD privé "Marie Goy", Vorey sur Arzon
- EHPAD privé "Saint-Joseph", Le Puy en Velay
- EHPAD public "Les Terrasses de la Gazeille", Le Monastier sur Gazeille
- EHPAD privé "Notre Dame", Beaulieu

Dr Cyril CORNILLE is infectious disease specialist for the French Haute Loire region and the coordinating physician for the multidisciplinary antibiotic therapy team of the Haute-Loire Groupement Hospitalier de Territoire (GHT). He works closely with the GHT's mobile hygiene team, and regularly visits all the study centers. He is the principal investigator for each of the 12 centers.

1.4. Study schedule

- Submission to the Ethics Review Board (*Comité de Protection des Personnes* – CPP): March 2024
- Information of the French *Agence Nationale de Sécurité des Médicaments* : September 2024
- Start date: October 1, 2024
- Follow-up for each period: 7 months + 30 additional days to monitor the evolution of ongoing ARI, hospitalization and AEI[2] at the end of the first 7 months
- End of study: May 31, 2026
- Total study duration: 20 months

[2] AEI: adverse event of interest

2. RATIONALE

2.1. Acute respiratory infections in the elderly

Acute respiratory infections (ARIs) include lower respiratory infections (involving the trachea, bronchi and lung parenchyma) and upper respiratory infections (involving the nasal cavities, sinuses, auditory canals, pharynx and larynx) [1]. Lower respiratory infections have the greatest impact on both the patients (in terms of morbidity and mortality) and the healthcare system [(1-5)].

ARIs are the leading cause of transfer to hospital and infectious mortality in Nursing Homes [6,7]. Studies have reported that 10-50% of residents with pneumonia need to be transferred to hospital, of whom 20-40% died [8-12]. According to Santé Publique France, the average attack rate of ARI among Nursing Homes residents in winter is 18% to 25% and the average case-fatality rate is 3%. According to the French High Council for Public Health (HCSP), the median incidence of lower respiratory infections in residential care facilities for the elderly is estimated at 1 episode per 1,000 resident-days. This incidence is 30 times higher than that observed in the general population and 10 times higher than that reported in the community-dwelling population aged 75 and over [14-16]. In an autopsy study published by Aronow *et al*, infectious diseases were the cause of 21% of deaths[17]. In another large series of 3,000 consecutive autopsies carried out in geriatric institutions in Geneva, infectious pathologies accounted for 55% of deaths, 60% of which were of pulmonary origin[18].

Nursing Home residents are mostly over 65 and suffer from multiple factors of fragility. Barnett *et al.* reported that, more than 50% of people over 65 had at least 2 comorbidity factors, rising to more than 75% of those over 80 [19]. In the Priam study[20] involving 44,869 residents in 578 Nursing Homes (mean age 86, 76% female), 49% were categorized as very dependent (GIR index* <3). Geriatric fragility has been studied by Fulop *et al.* [21], who described how a "stressor" may lead to an increasing number of cascading complications with advanced age, number of comorbidities, and number of medications that may mask the warning signs. The high risk of ARI complications for nursing homes residents is linked to this individual fragility but also to the organization of community life and the contagious nature of many respiratory infections (particularly viral). Nursing Home are, by their very nature, a place that favors the dissemination of infectious agents, despite the application of good practices and the proper use of anti-infectious agents [22,23]

The most common pathogens causing ARI in Nursing Home are :

- Viruses, including influenza viruses, respiratory syncitial virus (RSV), SARS-CoV-2 (Covid19) and others (parainfluenza, rhinovirus, human metapneumovirus, coronavirus, adenovirus), with very high attack rates and high mortality rates [24].
- Bacteria: Streptococcus pneumoniae, Legionella spp and Chlamydophila pneumoniae, with high mortality rates [24].

Part of the transmission of infectious agents responsible for ARI occurs through inhalation of contaminated micro-droplets [25-27]. The precautions recommended in the event of an epidemic (wearing a mask, individual isolation, eye protection for caregivers) are difficult to maintain

*GIR index: Groupe Iso-Ressource - dependency index: corresponds to the level of loss of autonomy of elderly people.

on a day-to-day basis, particularly in the case of residents with psychological or neurological disorders [28] .The impact of microdroplet transmission is difficult to study in the general population, due to the multiple social interactions occurring throughout the day, the variety of places frequented, and the mix of transmission modes: contact, ballistic droplets, microdroplets[29,30,31]. On the other hand, Nursing Homes offer the double advantage of being environments where these interactions are more controlled (few interactions with the outside world) and where the environment is more homogeneous (same residents, staff, uses, precautions vis-à-vis outsiders, etc.).

Nursing Homes are places that bring together people at risk of ARI, while also offering the right conditions to better understand them and study how to prevent them.

2.2. UltraViolet Germicidal Irradiation

Microdroplet transmission of respiratory diseases is the subject of intense research to determine the proportion of transmissions attributable to it. Demonstrating this transmission is difficult in humans, due to the large number of social interactions. Scientists were only able to determine that tuberculosis was a purely microdroplet-transmitted disease after numerous studies, notably that of Riley *et al.*[32] . Similarly, measles was not accepted as a microdroplet-transmitted disease until the 1970s, thanks in particular to the work of Wells [33] , Riley *et al.* [34] and Bloch *et al.* [35] . This transmission has not yet been clearly established for many respiratory pathogens, such as RSV, influenza and rhinoviruses, although there are many indications that this route could significantly contribute (RSV: Kulkarni *et al.* [36] ; influenza: Cowling *et al.* [27] ; rhinoviruses: Myatt *et al.* [37] ...). Similarly, microdroplet transmission of non-tuberculous bacteria has not been clearly established [38].

A Nursing Home is a relatively closed environment compared to others, such as schools (strong community mixing), offices or means of transport. This is an advantage for the study of microdroplet transmissions. As the number of interactions between participants is more limited, the risk of contamination by contact and ballistic droplets is reduced, and external inputs are more controlled (mainly staff and families). It should be noted that families, and even more so Nursing Home staff, are made aware of the risks of transmission they carry, which, without eliminating them, limits the external factor.

ARI transmission can be prevented in a number of ways, aimed at reducing the pathogen load in the air so that an infectious dose is not reached. This infectious dose depends on a number of factors, including the nature of the pathogen and people's immune sensitivity.

Strategies to limit the transmission of the most common ARIs are limiting pathogen emissions (masks), vaccination, and reducing pathogen load in the air. Three techniques are used to reduce pathogen load in the air: Adding fresh air (ventilation), air filtration (notably with HEPA filter systems), and inactivation of airborne pathogens through germicidal action.

Ventilation is measured in terms of air change rate, commonly expressed in ACH (Air Change per Hour, in m^3/h/occupant). An operating theatre should have an air renewal rate of between 15 and 50 m^3/h/occupant, depending on the category of surgery performed (risk zones defined in standard NF S 90-351). The French Code du Travail and Règlement Sanitaire Départemental Type define flow rates for offices (25m^3/h/occupant) and catering (30m^3/h/occupant). A special case concerns premises designed to isolate patients carrying infectious diseases, for which the WHO recommends 12 m^3/h/occupant [39] .

Few spaces have the ventilation capacity to reach such ACH values. Increasing flow rates is complex, costly and energy-intensive (heating, air conditioning, humidification). In addition, it is difficult to envisage continuous ventilation in nursing homes, for reasons of temperature, resident frailty, noise, pollution and patient safety. Ventilation is therefore used outside the presence of residents, after or before the time when the potential for contamination is greatest.

Filtration was intensively discussed during the Covid19 pandemic. The effectiveness of filtration systems systems depends on the filter's ability to trap pathogens, which means that only the air passing through the filter is decontaminated. The efficiency of these systems is therefore closely linked to the flow rate of the fan and the size of the room being treated. A refectory (8m x 10m x 2.4m, i.e. 192m3) requires a flow rate of 1150m^3/h at 6 ACH, 2300m^3/h at 12 ACH. Such flow rates imply high power consumption and noise levels (often in excess of 55dB), which often lead users to turn off the devices. There are also significant maintenance requirements: changing filters and pre-filters (1 to 2 times a year for each), and cleaning sensors (2 to 4 times a year). This maintenance is critical to system efficiency, and is often neglected.

Pathogen inactivation, the method chosen for this study, consists of eliminating pathogens from the air through germicidal action. Germicidal agents can be either gaseous (ozone, hydrogen peroxide, etc.) or luminous (germicidal light, UV-C). Although highly effective and widely used in other applications (e.g. water treatment), gaseous treatments must never be used in the presence of people. Germicidal light can be used in the presence of people if they are not exposed.

UVGI (UltraViolet Germicidal Irradiation) "Upper-Room" systems enable a germicidal zone to be created at the top of the room, well above people, without exposing them. The first UVGI devices were created in the USA in the 1930s. These devices are placed high up (2.20m from the floor) and treat exhaled air (which rises due to lung temperature being higher than ambient temperature) and circulating air (due to overall room convection) each time they pass through the upper zone. Their main objective is to combat microdroplet-transmitted infections. One of the first clinical studies was published by Wells *et al.* [40] , on school classes in Philadelphia. An 85% reduction in measles infections was reported. Since then, several animal and human clinical studies have been carried out to study the effectiveness of UVGI system in reducing the risk of infectious diseases[41-54], most of them non-randomized and conducted with first-generation devices.

2.3. Hypotheses

While UVGI is biologically plausible and supported by strong laboratory data, there is a lack of contemporary randomized controlled trials in real-world environments

We therefore pose the following hypothesis: The use of Upper-Room UVGI air decontamination systems in nursing homes could reduce the incidence of ARIs, as well as the risk of complications and hospitalization.

In order to test this hypothesis, we will compare the incidence of ARI during two winter periods between residents of Nursing Homes equipped with active UVGI systems and Nursing Homes equipped with inactive (control) systems. We will also assess the impact of UVGI on the severity of ARI,[55] antibiotic consumption, microbiological air quality, pathogen deposition on test surfaces, as well as the potential medico-economic benefits of using UVGI devices.[56]

2.4. Known and foreseeable benefits and risks

2.4.1. Expected benefits for participants

We expect a reduction in the incidence and severity of ARIs in Nursing Home equipped with UVGI.

2.4.2. Expected risks for participants

The risks for residents is expected to be very low (very rare frequency, slight to moderate severity). They lie in the exposure of people to UV-C rays. Due to its design and position, the UVGI device should not directly expose residents to UV-C radiation.

The installations of the devices will be checked and exposure measurements will be taken to ensure user safety, in accordance with Directive 2006/25/EC of the European Parliament and of the Council of 5 April 2006 on health and safety requirements regarding the exposure of workers to the risks arising from physical agents (artificial optical radiation). Explanatory and informative signs will be displayed in each area equipped with the devices (see section 18.1 Installation of UVGI air treatment systems).

The risks of exposure to UV-C include skin damage (erythema*) and eye damage (photokeratitis) after long direct exposure (45 minutes)[57]. These phenomena are reversible within 48 hours [58].

A double-blind study of more than 3,000 people followed over 9 years with 1,400 upper-room devices such as those we will use in this study, showed no side effects during normal use of UVGI compared with a placebo period [59].

2.5. Expected benefits for the population

UVGI air treatment systems are not recommended in France, even for frail individuals such as the elderly living in nursing homes.

This study will provide concrete evidence of the interest and relevance of UVGI systems in nursing homes.

3. STUDY CHARACTERISTICS

3.1. Type of study

This is a multicenter open-cohort, cluster-randomized crossover, quadruple-blind placebo-controlled trial.

3.2. Research category and constraints for participants

This trial evaluates a device to complement standard care for Nursing Home residents. It is classified as category 2 research involving human beings (RIPH-2) under French law.

The risk for participants is UV overexposure resulting in mild adverse events (photokeratitis and erythema, both reversible without treatment). This risk is considered very low.

* Erythema of interest is linked to UV-C exposure (face, neck, hands, forearms, etc.), and can be distinguished from contact erythema, which is common in the elderly (buttocks, heels, elbows, legs, etc.).

3.3. Study diagram

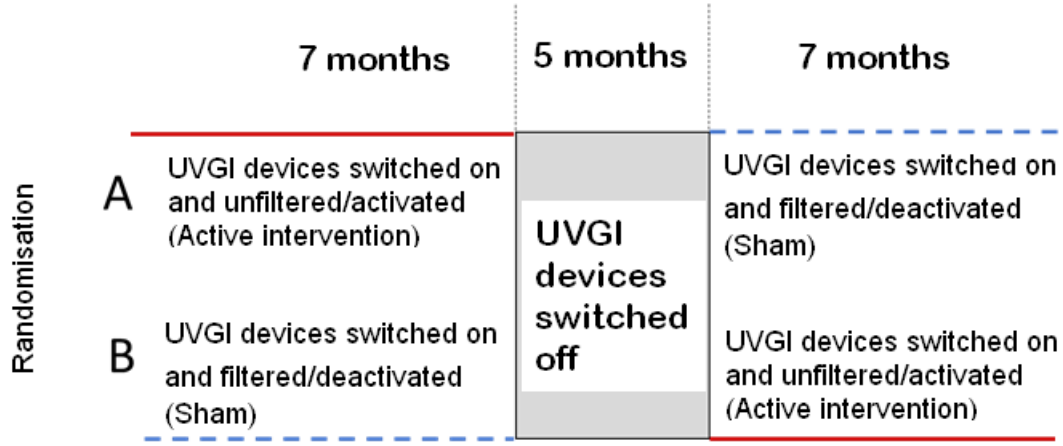
The study assesses the benefits of UVGI devices placed in communal living spaces to reduce the incidence and severity of ARI in Nursing Home residents. In all the Nursing Homes included, UVGI devices will be installed and commissioned at the start of the study. Some UVGI devices will be deactivated by installing an invisible internal filter. The inactivation filters will be installed by a technical team independent of the investigation team. Inactivation will therefore be carried out blind to the study team, care givers and statistician.

Participating Nursing Homes will be randomized into two arms:

- In arm A: UVGI devices will be left active during period 1, and filtered (i.e. deactivated) during period 2.
- In arm B: UVGI devices will be filtered (i.e. deactivated) during period 1 and will remain active during period 2.

The two periods will last 7 months each, and will take place two years in a row on the same dates (October 1 to April 30). They will be separated by a 5-month wash-out period (May 1 to September 30), during which all UVGI devices will be switched off in both arms.

Figure1 . Study diagram



3.4. Randomization

The centers included will be randomized into arms A and B in a 1:1 ratio, using a centralized computerized system.

4. STUDY OBJECTIVES AND EVALUATION CRITERIA

4.1. Primay objective

The primary objective is to compare the incidence of severe acute upper and lower respiratory infections, between periods when Nursing Homes are equipped with active UVGI systems and periods when Nursing Homes are equipped with inactive UVGI systems.

4.2. Secondary objectives

The secondary objectives are to compare, between periods when the Nursing Homes are equipped with active UVGI systems and periods when the Nursing Homes are equipped with inactive UVGI systems:

7. The incidence of acute respiratory infections, all grade of severity combined
8. The incidence of all-cause hospitalization or death
9. The incidence of adverse events of interest, overall and by severity grade
10. The consumption of antibiotics
11. The presence of pathogens in the air and on test surfaces (fomites)*
12. The medico-economic benefits of installing UVGI systems

4.3. Primary endpoint

The primary endpoint is the incidence of severe* symptomatic acute upper and lower respiratory infections†, all grades of severity combined.

* Severe = leading to oxygen therapy, hospitalization or death

(†) Acute infections considered include sinusitis, otitis media, nasopharyngitis, angina, tracheitis, bronchitis, pulmonary abscess, pneumonia and COPD exacerbations. Documented symptomatic infection with SARS-Cov-2, influenza virus, or respiratory syncytial virus, will be considered by default as a respiratory infection, even in the case of dominant extra-respiratory symptoms.

4.4. Secondary endpoints

The secondary endpoints are:

1. Incidence of symptomatic ARIs of any severity
2. Incidence of non-infectious adverse events of interest††, overall and by severity grade (CTCAE classification)
3. Incidence of all-cause hospitalization or death (separately and combined)
4. Total antibiotic consumption, overall and by class
5. Viral load in air samples collected in communal living spaces
6. Viral, bacterial and fungal load on surface (fomite) samples collected in communal living areas
7. Incremental Cost-Effectiveness Ratio (ICER) of UVGI implementation.

(††) Keratitis and erythematous skin eruptions occurring in light-exposed areas.

5. STUDY POPULATION

5.1. Inclusion criteria

Inclusion of centers:

Nursing homes:

* Fomite = Inert object that can carry infectious agents, passive vector for disease transmission

- Having a system for monitoring cases of upper and lower respiratory infections in their residents
- Agreeing to take part in the study
- Undertaking to comply with the entire protocol
- Accepting the installation of UVGI devices
- Undertaking to provide all residents or their legal guardians/curators with an individual information leaflet

Inclusion of individuals

All residents who have at least one day's presence in one of the participating centers during one of the two calendar periods of the study (period 1: between October 1, 2024 and April 30, 2025; period 2: between October 1, 2025 and April 30, 2026) will be eligible.

5.2. Exclusion criteria

Exclusion of centers:

Nursing Homes will not be included in the study if:

- They are already equipped with another air treatment system (i.e. HEPA* , ionization) in common living spaces
- They do not wish to be equipped in all the spaces needing to be equipped according to the trial coordinating investigator
- They have planned a major change to the structure (extension, renovation, closure, requalification, etc.) that could affect the study population and/or UVGI air treatment systems during the course of the study.

Exclusion of individuals:

Residents of participating centers who have expressed (personally or through a relative or legal representative) a wish that their personal data not be used for the study at any time between the start of the study and the analysis of the results will not be included in the study.

5.3. Recruitment

All residents of the partipating Nursing Homes will be informed of the study by the study coordination team and the Nursing Home care team.

5.4. Information and opt-out

This study falls within the scope of Article L1122-1-4 of French law no. 2012-300 of March 5, 2012 ("loi Jardé"), which stipulates that "*in the case of research whose methodological requirements are not compatible with the collection of consent under the conditions provided for in the second paragraph of Article L. 1122-1-1, the protocol submitted for the opinion of the relevant personal data protection committee may stipulate that consent is not sought [...]. No research mentioned in the first paragraph may be carried out on a person if he or she has opposed it".*

* High Efficiency Particulate Air= very high density particulate air filter

Residents will be fully and fairly informed, in comprehensible terms, of the principles, objectives, constraints and expected benefits of the study. This information will be provided in the form of an individual written information notice, which will be given or sent to residents, their relatives and/or their legal representatives. This information notice will explain residents' right to object at any time to the collection of their personal data. Nursing staff and study coordinators will be available to answer residents' questions at any time.

Only documents approved by the ethics committee will be used for this study, in their latest version, to the exclusion of any other document.

No data will be collected if the resident or his/her representative expresses his/her opposition. If this objection is notified after the collection of personal data has begun, previously collected data will be deleted.

5.5. Exclusion period and participation in other research

For the duration of their participation in the RESPROTECT study, residents may only participate in other interventional or observational studies that do not influence the occurrence, treatment or management of respiratory infections. The RESPROTECT sponsor must be consulted prior to inclusion in any other study.

Once their participation in the RESPROTECT study has come to an end (due to scheduled study termination or premature discharge), residents will be able to participate in other studies without delay.

5.6. Volunteer compensation

No compensation is planned for this study.

6. PROTOCOL PROCEDURES

6.1. UVGI air treatment systems

The UVGI devices will be installed prior to the start of the study by a team of independent contractors, in accordance with the installation protocols described in paragraph 18.1.

This team will then carry out a commissioning visit before the start of the 1st period, followed by a maintenance visit during the wash-out period before the start of the 2nd period.

The deactivation filters will be:

- Installed in arm B during the commissioning visit, and removed during the maintenance visit.
- Installed in arm A during the maintenance visit.

Residents, Nursing Home staff, investigators, and members of the clinical trial unit in charge of data collection or processing will not be informed of the presence of the filters.

In all centers, UVGI devices will be switched on the day of the start of the 1st period, switched off on the day after the end of the 1st period, switched on again on the day of the start of the 2nd period and switched off again on the day after the end of the 2nd period. They will remain lit continuously during both periods. They may be turned off temporarily in the event of work being carried out on the ceiling.

6.2. Clinical and microbiological monitoring

6.2.1. Time T0

Time T0 corresponds to the period between informing residents and turning on the UVGI air treatment units.

The study coordinating team will explain to caregivers how to set up and use the UVGI equipment, and how to collect clinical, paraclinical and microbiological data throughout the study.

6.2.2. Time T1

Time T1 corresponds to the 1st experimental phase (October 1st 2024 to April 30 2025).

Baseline data

Baseline data for all participants will be collected from Nursing Home records and entered into the eCRF.

Morbidity episodes and mortality

Nursing staff will be responsible for monitoring the occurrence of respiratory infections and adverse events of interest, as well as reporting hospitalizations and deaths.

The occurrence of ARIs, AEIs, all-cause hospitalizations, and all-cause deaths will be reported weekly to the trial's clinical research assistants (CRAs) by a designated contact person at each center. The clinical features, as well as any additional examinations prescribed and their results, will be noted in the resident's medical record. CRAs will verify individual reports against predefined diagnostic criteria in the resident's record (and, in case of hospitalisation, in the hospital record) and classify each event as validated (criteria met), rejected (criteria not met), or deferred (uncertain classification pending review). The Clinical Event Review Committee (see section 9.4) will adjudicate deferred events and systematically review all hospitalization and death records. Validated events will be entered into the eCRF by the Clinical Research Assistants (CRAs).

CRAs and the CERC will have secure online access to the electronic care records of participating nursing homes and to hospital records for hospitalized residents. To ensure completeness of event collection, the nursing home software will be queried every three months to generate comprehensive lists of all discharges (death, hospitalization, return home, or transfer to another facility), as well as oxygen and anti-infective prescriptions. These data will be cross-checked against the study database, and any missing or inconsistent events will be investigated and adjudicated by the CERC, in accordance with best practices for independent endpoint review committees

Microbiological monitoring of air and surfaces

Environmental monitoring will be performed to quantify pathogen contamination in the air and on surfaces within nursing home communal areas. Air and surface samples will be collected at baseline and every seven weeks during both study periods.

Air samples will be obtained using volumetric air samplers operating at standardized flow rates. Surface samples will be collected using tryptic soy agar (TSA) contact plates and sterile polyester-headed swabs (eSWAB) applied to predefined fomites. Two self-adhesive plastic fomites will be installed in each center — one in a dining room and one in a communal activity room.

Air samples will be analyzed by quantitative PCR (qPCR) assays targeting SARS-CoV-2, influenza A and B viruses, and respiratory syncytial virus, using the *Triplex Thermo Fisher TaqPath COVID-19, FluA/B, RSV Combo Kit* (Ref. A49867). Surface samples will be processed for bacterial and fungal detection by culture on TSA plates, followed by species identification using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS, Bruker Daltonics). Viral detection from fomites will be performed by qPCR (see details in section 18.2).

6.2.3. Time T2

Time T2 corresponds to the wash-out period (April 1 to September 30, 2025).

During this phase, all UVGI devices will be turned off. No microbiological sampling of air or surfaces will be carried out. ARI and AES will not be monitored. Deaths, hospitalisations and opt-out request will continue to be monitored. New participants will be informed on the study, and their baseline data will be recorded.

6.2.1. Time T3

Time T3 corresponds to the 2nd experimental phase (October 1, 2025 to April 30, 2026). During this period, clinical, paraclinical and microbiological data will be collected in the same way as during T1.

6.2.2. Time T4

Deaths and hospitalizations will continue to be monitored until May 31, 2026, in order to characterize any possible death or hospitalization occurring after the end of the 2nd period but possibly linked to an ARI or an AE that began before the end of the 2nd period.

6.3. Monitoring summary table

Table 1. Follow-up of centers and individuals participating in the research

	T0 (Sept 2024)	T1 (Oct 2024-Apr 2025)	T2 (May 2025-Sept 2025)	T3 (Oct 2025-Apr 2026)
Individual information of 'prevalent' residents	x			
Individual information of 'incident' residents		x	x	x
Collection of opt-out requests	x	x	x	x
UVGI system implemented	x			
UVGI systems filtered/unfiltered, according to randomization	0/x		x/0	
UVGI systems turned on		x		x
UVGI systems turned off	x		x	
Collection of baseline data from 'prevalent' residents	x			
Collection of baseline data from 'incident' residents		x	x	x
Monitoring of ARI[a] and AEI[b]		x		x
Monitoring of discharge, hospitalization and death		x	x	x
Pathogen sampling on test and air surfaces		x		x

[a] ARI: upper respiratory infection (sinusitis, otitis media, nasopharyngitis, angina, tracheitis) and lower respiratory infection (bronchitis, pneumonia and COPD exacerbations). Symptomatic infection with SARS-Cov-2, influenza

or Respiratory Syncytial Virus will be considered by default as a respiratory infection, even in the case of dominant extra-respiratory symptoms.

[b] AEI: adverse event of interest (keratitis and erythema in exposed areas)

6.4. Premature study termination

6.4.1. Opposition to data collection

Residents will have the right to object to the use of their data at any time, without having to give reasons, and without this having any adverse effect on their surveillance and care. In the event of opposition to the collection of their data, care vigilance will continue and potential adverse events of interest will continue to be reported

6.4.2. Study premature termination

In the event of premature termination or suspension of the study by the sponsor, the latter will immediately inform the investigators, the centers, the competent authorities and the Ethics Committee of the termination or suspension of the study and the reasons for it.

6.5. Data collected

Study data will be transcribed by the healthcare staff involved in a clear and legible way in the source documents (medical records) and collected in the electronic case report form (eCRF) by the clinical research assistants who will electronically sign the case reports.
The information gathered for this study will be as follows:

6.5.1. Participants data

<u>Baseline</u>

- Investigating center code (automatic)
- Participant ID number (automatic)
- Participant date of birth (month/year)
- Gender
- Date of information on the study
- Date of inclusion in the study
- Dependency index : AG-GIR (Autonomie Gérontologie Groupes Iso Ressources) score
- Vaccination status (Covid19, Influenza, Pneumococcal)
- Comorbidities

<u>Follow-up</u>

- Date(s) and reasons for hospitalization
- Date and cause of death
- Date(s) and reason(s) for leaving (and re-entering, if applicable) the center
- IRA or AEI episodes
  - Symptoms
  - Additional tests
  - Diagnosis

- Antibacterial and antiviral treatments
- Hospitalizations
- Oxygen treatement
- Event outcome

- Vaccinations

6.5.2. Center data

- Pathogens isolated in air and surface sampling
- Antibiotic consumption
- Characteristics of the ENH: number of residents, number of staffs.
- Significant modification of hygiene and care protocols, where applicable.
- Unforeseen change to the structure (e.g. fire, water damage, etc.) that could lead to a major modification of the structure (extension, renovation, closure, requalification, etc.) that could affect the study population and/or UVGI air treatment devices, during the course of the study.

7. STATISTICAL CONSIDERATIONS

7.1. Number of centers and individuals to include

Each Nursing Home will have an approximate size of 90 participants, with a small coefficient of variation. It is estimated that 80% of participants will be present in both periods. As recruitment is open to new participants, those who die or permanently leave their Nursing Home will be replaced, and the number of participants present in each Nursing Home will remain constant throughout the study.

The intra-cluster coefficient of variation (WP-ICC ρ) is estimated at 0.1 (10% of ARIs are explained by the Nursing Home environment). The inter-period correlation (between-period ICC η) is estimated to be negligible (the two periods are winter and one year apart). Cluster auto-correlation (CAC) is set at 0.5 (i.e. η=0.05), a figure recommended when few hypotheses are involved (Giraudeau *et al*, Sample size calculation for cluster randomized cross-over trials. Stat Med 2008;27:5578-85). Individual auto-correlation (IAC) is set at 0.2. Assuming an ARI incidence of 17 per 100 patient-years in the absence of UVCI devices, it is estimated that 12 clusters need to be included to demonstrate a 50% reduction in ARI incidence, with a two-sided alpha risk of 0.05 and power of 80% (Kasza *et al*, Sample Size Calculation for Stepped Wedge and Other Longitudinal Cluster Randomised Trials. Stat Med 2020;39:1871-83; Hooper *et al*, Sample size and power calculations for open cohort longitudinal cluster randomized trials. Stat Med 2016;35:4718-28)

7.2. Data analysis

Details of the analysis methods will be set out in a specific document entitled "analysis plan", validated by the study's scientific board and made public before the start of the analysis.

The principles guiding the drafting of this analysis plan will be as follows:

<u>General</u>

- The analysis will be performed on an intention-to-treat basis, and will include all centers and all permanent residents, whatever their length of follow-up and reason for premature discharge from the center, with the exception of those who opted out.
- A two-tailed *p-value* of <0.05 is considered statistically significant.

Main analysis

The main comparison will focus on the incidence of first severe ARI between follow-up periods with an unfiltered UV device and follow-up periods with a filtered UV device. The numerator will be the number of people who experienced at least one severe ARI during a period. The denominator will be the cumulative time spent in the nursing home until the first ARI or exit from the period.

The result will be expressed as an incidence ratio with a 95% confidence interval.

In the first instance, the analysis will be carried out at the individual level. A generalized linear mixed model will be used, with a Poisson distribution or a negative binomial distribution in the case of overdispersion, a logarithmic link function and an *offset* term for the number of patient-years. The model will take into account not only intervention and period fixed effects, but also random effects at cluster, cluster-period, cluster-individual and individual levels. The correlation structure will be of the exchangeable block type.

In the second instance, if the model does not converge, we will perform the analysis at the cluster level (Hayes RJ, Moulton LH. *Cluster Randomised Trials*. CRC Press; 2017. https://books.google.fr/books?id=ikIrDwAAQBAJ p197).

Sensitivity analyses will be carried out:

- Using the cumulative incidence of severe ARI as the endpoint, with the total number of severe ARI in the numerator and the cumulative time spent in the nursing home until exit from the period in the denominator. The model will be the same as the main model, with the addition of a random individual-period effect.
- By adjusting the model on the following variables: gender, age, GIR index. The last two variables will be measured at the start of each period.

Analysis of clinical secondary endpoints

- Analyses of clinical secondary endpoints will focus on:
  - Incidence of symptomatic ARIs of all grades
  - Incidence of all-cause hospitalization, all-cause mortality, and all-cause "hospitalization or death"
  - Incidence of non-infectious adverse events of interest, overall and by severity grade (CTCAE classification).
- Analyses of clinical secondary endpoints will focus on the occurrence of the 1st event and will be performed without adjustment. Sensitivity analyses will be performed:
  - Using cumulative incidence as the endpoint
  - By adjusting the model on the following variables: age, gender, GIR index.
- Analyses of clinical secondary endpoints will use the same model as that used for the primary analysis, or equivalent models appropriate to the frequency of events.

Analysis of microbiological secondary endpoints

These secondary analyses will compare microbiological loads in air and fomite samples between periods when UVGI devices are unfiltered (active) versus filtered (inactive). The outcome will be expressed as cycle threshold (Ct) values and number of genome copies/m^3 for viral agents; and colony-forming units (CFU)/cm^2 for bacterial and fungal agents. Mean microbial loads will be compared using mixed-effects linear regression models, including random effects for cluster and period.

Subgroup analysis

Depending on clinical relevance, exploratory subgroup analyses may be proposed after studying the subgroup × arm interaction in the above-mentioned regression models.

Missing data

For explanatory variables missing in less than 10% of participants, and verifying the hypothesis of the random nature of this loss of information, multiple imputation may be proposed. For explanatory variables missing in more than 10% of residents, no imputation will be performed and these covariates will not be included in multivariate analyses.

Intermediate analysis

No interim analysis is planned for this study. The Data and Safety Monitoring Board may request a parallel exploratory analysis (group A vs. group B) after the end of the 1st period if it wishes to explore the hypothesis of premature evidence of efficacy or futility. If an analysis is performed for efficacy, the Haybittle-Peto stopping rule will be used: p-value=0.0027. This rule being conservative, the significance level would remain at α=5% for the final analysis.

Other points to watch

The DSMB will be vigilant for the emergence of signs suggestive of toxicity, even if the evidence currently available strongly suggests that the risk of toxicity is very low.

The DSMB will pay particular attention to the appropriateness of the choice of the primary endpoint. When the study was designed, the investigators hesitated between choosing a broad primary endpoint including all high and low ARIs, whatever their severity, and a more restrictive primary endpoint including only severe low ARIs. Uncertainty was linked in particular to the absence of reliable recent data allowing to estimate the impact of either of these two options on the trial conduct. The DSMB will assess the relevance of the chosen primary endpoint in the light of the incidence observed, and may, if it so wishes, recommend a change in the definition of this endpoint, provided that the arguments presented for this change do not call into question the principle of quadruple blinding.

8. RISK MANAGEMENT

8.1. Managing adverse events

8.1.1. Definitions

Adverse event (AE):

An adverse event is any harmful manifestation occurring in a person participating in a study, whether or not this manifestation is related to the research or to the product on which the research is focused (*R1123-46 of the French CSP; amended by Decree n°2016-1537 of November 16, 2016 - art. 10 and 14).*

Serious adverse event (SAE) :

A serious adverse event is one that:

- leads to death,
- endangers the life of the participant,
- requires hospitalization or prolongation of hospitalization,
- causes significant or lasting disability or handicap,
- is a congenital anomaly or malformation.

(*R1123-46 of the French CSP; amended by Decree no. 2016-1537 of November 16, 2016 - art. 10 and 14*)

AE of interest (EII)

For this study, the adverse events of interest are erythema in light-exposed areas and keratitis.

Severity criteria :

The severity of events will be classified according to CTCAE classification version 5.0 (grade 1 to 5).

The severity of events not listed in this classification will be assessed according to the following qualitative criteria:

- Mild (grade 1): does not affect the participant's daily activities,
- Moderate (grade 2): disrupts the participant's 's usual daily activities,
- Severe (grade 3): prevents the participant's 's usual daily activities,
- Very severe (grade 4): requires resuscitation/life-threatening,
- Death (grade 5).

8.1.2. Notification of serious adverse events *(SAEs)*

No AE or SAE will be reported to the sponsor, in accordance to the French regulation applying to studies classified as category 2 RIPH.

9. MONITORING

9.1. Scientific Advisory Board

9.1.1. Composition

It is made up of the coordinating investigator, the trial statistician, the Director of the CTU, the scientific referent, the project manager and 3 external expert members appointed by the sponsor. It is chaired by one of the external members chosen by his peers.

9.1.2. Pace of meetings

The Scientific Advisory Board meets twice a year until the research is completed.

An extraordinary meeting may be called at any time by decision of the Chairperson of the Scientific Advisory Board, or at the request of the Coordinating Investigator or the sponsor.

9.1.3. Role

The Scientific Advisory Board's mission is to ensure that the research is carried out appropriately, from a scientific, ethical and logistical point of view.

- It ensures that the research runs smoothly and that the protocol is respected,
- It ensures that all investigators and other research participants are kept informed,
- It ensures the scientific follow-up of the research: maintaining the relevance of the research questions and the validity of the methods used to answer them,
- It oversees the application of rules governing access to research data and the communication and publication of research results,
- It maintains a permanent link with the sponsor and the DSMB,
- It decides on any relevant modifications to the protocol necessary for the continuation of the research, in particular:
  - Amendments to the protocol,
  - Decisions to open or close study sites.

9.2. Data and Safety Monitoring Board

9.2.1. Composition

It is made up of 3 external expert members appointed by the sponsor, chosen for their expertise in clinical research.

9.2.2. Pace of meetings

The DSMB meets regularly throughout the trial, on its own initiative or at the request of the coordinating investigator, the trial's Scientific Advisory Board or the sponsor. At least one meeting per year is desirable.

9.2.3. Role

The DSMB has an advisory role for the sponsor, the coordinating investigator and the Scientific Advisory Board. It gives a general opinion on the progress of the trial. It can help to make difficult decisions during the course of the trial, for which an independent judgment is desirable. In particular, it advises on :

- Premature termination of the trial (due to toxicity or futility, because the trial is no longer feasible, or because the elements needed to reach a conclusion have already been gathered);
- Extensive modifications to the protocol that may become necessary to take account new scientific data;
- Interpretation of analysis results or need for intermediate analysis.

The opinion of the DSMB is sent in writing to the Coordinating Investigator, the Sponsor, and the Chairperson of the Scientific Advisory Board.

9.3. Steering Committee

9.3.1. Composition

It is made up of all the project team members listed on page 12.**Erreur ! Source du renvoi introuvable.**

9.3.2. Meeting schedule

The steering committee meets weekly at the start of the study, and then at intervals as required.

9.3.3. Role

The role of this committee is to supervise and monitor the progress of the trial.

9.4. Clinical Event Review Committee (CERC)

9.4.1. Composition

It is made up of the coordinating investigator, the scientific referent and the Clinical Reseach Assistants.

9.4.2. Meeting schedule

The CERC meets weekly.

9.4.3. Role

The role of this committee is to ensure that the documentation of morbidity events occurring during the trial is standardized. It is responsible for the following tasks:

- Validation of the procedure for collecting data on morbidity events;
- Advice to investigators on questions relating to the application of definitions and classification of morbidity events.
- Adjudicate events deferred by the CRAs
- Systematically review all hospitalization and death records

10. RIGHT OF ACCESS TO SOURCE DATA AND DOCUMENTS

10.1. Data access

The sponsor is responsible for obtaining the agreement of all parties involved in the research, in order to guarantee direct access to all source data for quality control and audit purposes, in accordance with articles L.1121-3 and R.5121-13 of the French Public Health Code.

Individuals participating in this research will be informed of their right to access, verify, correct, limit or oppose the processing and transmission of data concerning them, and of the procedures for applying this right*, via* the information leaflet. The sponsor undertakes to respond to any request for access to data within a maximum of 1 month.

10.2. Source data

Source documents, defined as any original document or object that can be used to prove the existence or accuracy of data or facts recorded during the study, will be kept by the investigators after the end of the study for a period of time that complies with French regulations.

10.3. Data confidentiality

In accordance with articles L.1121-3 and R. 5121-13 of the French Public Health Code and 226-13 and 226-14 of the French penal code, the sponsor and study investigators will take all necessary precautions to ensure the confidentiality of information concerning the trial and the persons taking part in it.

The rules of confidentiality will be made clear to Nursing Home residents taking part in the research, orally and in the study information leaflet.

The sponsor will ensure that participants in the research has not objected to the collection of their personal data.

Data collected *via* the eCRF, will be rendered anonymous using participants ID code. In participating centers, a table of correspondence between ID codes and participants names will be kept under the Principal Investigator's responsibility for a period of time in line with current regulations. Participants date of birth will be partially collected (month and year).

Identifiable data will be accessible only to study investigators and qualified personnel responsible for the conduct of the study, as well as to reviewers designated by the sponsor to ensure data accuracy and to members of regulatory bodies legally authorized to have access to the data.

All data will be collected in accordance with the reference methodology MR003established by the French Commission Nationale de l'Informatique et des Libertés.

11. DATA PROPERTIES

The study sponsor is the owner of the data. No use of the data or transmission to a third party should be made without its agreement.

12. QUALITY CONTROL AND ASSURANCE

12.1. Investigator and sponsor commitment

The sponsor and coordinators undertake that the study will be carried out in compliance with French regulations, good clinical practices and the World Medical Association's Declaration of Helsinki.

The investigators will certify that they have read all pages of the protocol. The coordinating investigator will ensure that all investigators and other qualified members of his team have access to the updated versions of the protocol and other documents relating to the conduct of the study.

12.2. External monitoring

A monitor will be appointed by the sponsor to ensure that the study is carried out properly, and that the data generated are documented, recorded and reported in accordance with the protocol and in compliance with regulatory requirements.

Subject to the agreement of the persons concerned, monitors duly mandated for this purpose by the sponsor will have access to the individual data necessary for this control; they are subject to professional secrecy. All visits and contacts will be the subject of a written monitoring report.

Monitoring procedures will be defined in accordance with risk-based monitoring guidelines. A monitoring plan will list the points to be monitored and the verification procedures. A set-up and closing visit will be organized for each participating center.

12.3. Audits and inspections

The study may be subject to audits or inspections that may apply to all stages of the study, from protocol development to publication of results and archiving of data used or produced as part of the study. All data, documents and reports are subject to audit or inspection.

The sponsor and participating centers should be able to give inspectors or auditors access to the data. Participating centers will agree to comply with the requirements of the sponsor and the competent Authority regarding an audit or inspection of the study.

12.4. Case Report Forms

All information required by the protocol will be recorded using electronic case report form (eCRF). The eCRF software will comply with FDA recommendations concerning computerized systems for clinical trial management and electronic signature, and with standards (CDISC, ICH, GCP 2001/20/CE).

13. ETHICAL CONSIDERATIONS

13.1. Comité de Protection des Personnes

The protocol and individual information notices will be submitted for approval to the CPP (Committee for the Protection of Persons) designated by drawing lots in accordance with French regulations..

The study summary and the CPP opinion will be sent by the sponsor to the French National Agency for the Safety of Medicines and Health Products (ANSM) for information before the start of the study.

13.2. Protocol amendments

All amendments to the protocol will be the subject of a new review from the CPP.

13.3. Support for research

All additional costs related to the research will be covered by the sponsor. This includes:

- Supply and maintenance of UVGI equipment during the study,
- Air and surface pathogen sampling and analysis by Multiplex PCR,
- Program coordination,
- Other clinical research costs

14. DATA PROCESSING AND STORAGE AND DOCUMENTS

14.1. Data capture and processing

Clinical Research Forms (CRF) will be accessible online. Entering, viewing or modifying data will only be possible via this eCRF.

Each user will be given a unique login and password, according to their role and responsibilities in the study. Each person authorized to access the eCRF:

- Will be identified in the table of delegated responsibilities for each center;
- Will have a "user" account with specific IT rights linked to its role.

An audit function will be integrated, enabling traceability of the data collected, as well as any modifications made (addition, modification or deletion of data). These modifications will be recorded in a non-modifiable electronic file (audit trail). The audit function will also identify the person who made the modification, as well as the date.

14.2. Data protection

This study falls within the scope of the "Reference Methodology 003" (MR-003) of the French National Commission for Information Technology and Civil Liberties (CNIL), in application of the French law of August 6, 2004 relating to the protection of individuals with regard to the processing of personal data. The sponsor undertaking to comply to MR-003 is registered under no. 2214314, signed by sponsor on July 8, 2019.

14.3. Archiving

The following documents will be archived in the clinical research unit of the CH Emile Roux until the end of the period of practical use.

- Protocol and amendments
- Procedures, monitoring plan, statistical analysis plan
- Individual data
- Reports of opening, monitoring and close-out visits
- SAB, DSMB, and steering committee Meeting reports
- Statistical analysis and final study report.

At the end of the period of practical use, all documents to be archived will be transferred to the general clinical research archives, under the responsibility of the sponsor, for a period in line with French regulation (currently 15 years after the end of the study)

No removal or destruction can be carried out without the sponsor’s agreement. At the end of this period, the sponsor will be consulted for destruction.

15. INSURANCE

In accordance with regulatory provisions, the sponsor has taken out civil liability insurance with *Relyens* to cover any damage resulting from the research.

Failure to comply with the legal conditions for research (absence of CPP opinion, opposition from the person, continuation of suspended or prohibited research) is a clause excluding coverage.

16. COMMUNICATION AND PUBLICATIONS

The study will be registered on *Clinical trials.gov.*

The final research report will be written by the study manager in collaboration with the coordinating investigator, the head of the sponsor's clinical research unit and the biostatistician in charge of the study. The final version will be sent to the sponsor, the

competent authority and the CPP within 6 months after the end of the 2nd follow-up period. This delay is reduced to 90 days in the event of premature termination of the research.

Results will only be disclosed with the prior joint agreement of the coordinating investigator, the Scientific Advisory Board and the sponsor. Results will be communicated and published. A report on the overall results of the study will be issued, for transmission by the investigator to residents and caregivers.

The rules for publication and authorization of papers and articles will be set out in a transparent plan approved by the Scientific Advisory Board.

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18. APPENDICES

18.1. Installation of UVGI air treatment systems

The installation protocol comprises 3 phases:
Phase 1: Implementation
Phase 2: Physical installation
Phase 3: Verification and validation of installations (commissioning)

Phase 1: Implementation

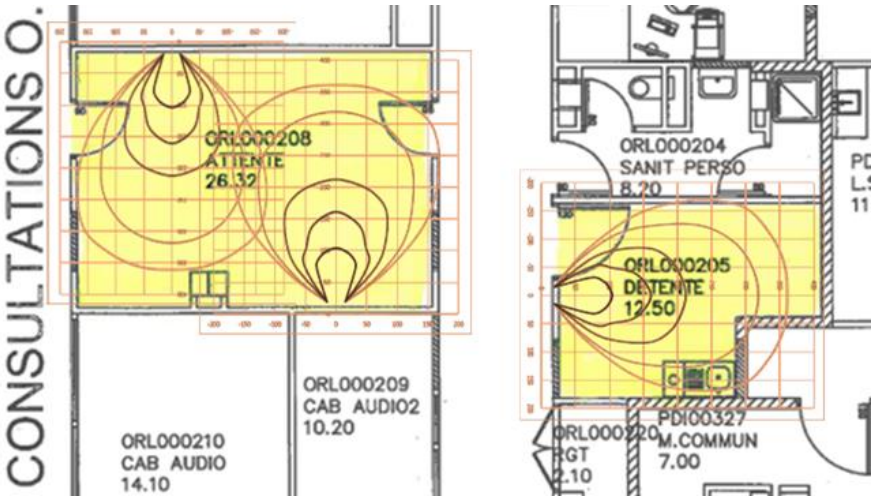
Phase 1 is used to validate the possibility of installing air treatment devices in the chosen locations, and to determine the positions of the various devices to ensure even distribution and protection.

This phase is divided into several stages:

- Stage 1: Collection and study of plans of the areas to be treated. This stage enables us to select the relevant locations for the intervention, including living areas (refectory, lounges, PASA, etc.), treatment areas (treatment rooms, infirmary, etc.), and areas shared by staff (break rooms, dressing rooms, etc.), and to calculate the number of devices required. This phase is carried out in consultation with Nursing Home managers, to guarantee the acceptability of the devices.
- Stage 2: visit to centers to check part heights, part geometry (plans sometimes not updated) and the presence of accessories or difficulties making installation impossible. Exclusion of non-compliant centers.
- Stage 3: New implementation proposal following inspection of the centers. Validation by the clinical research team and local center teams.

This phase will be carried out in cooperation with the supplier / service provider chosen to supply the air treatment devices. This cooperation is essential, given the wide range of characteristics of the devices on the market, with their different power ratings and radiation patterns.

Example installation: patient waiting room and caregiver break room



Phase 2: Physical installation

This phase includes the actual installation of the devices. This installation is carried out by the technical departments of the ENH, who are best placed to carry out the installation thanks to their knowledge of wiring and the specific features of the premises. The devices will be installed so that they can be switched on 24/24.

Phase 3: Verification and validation of installations

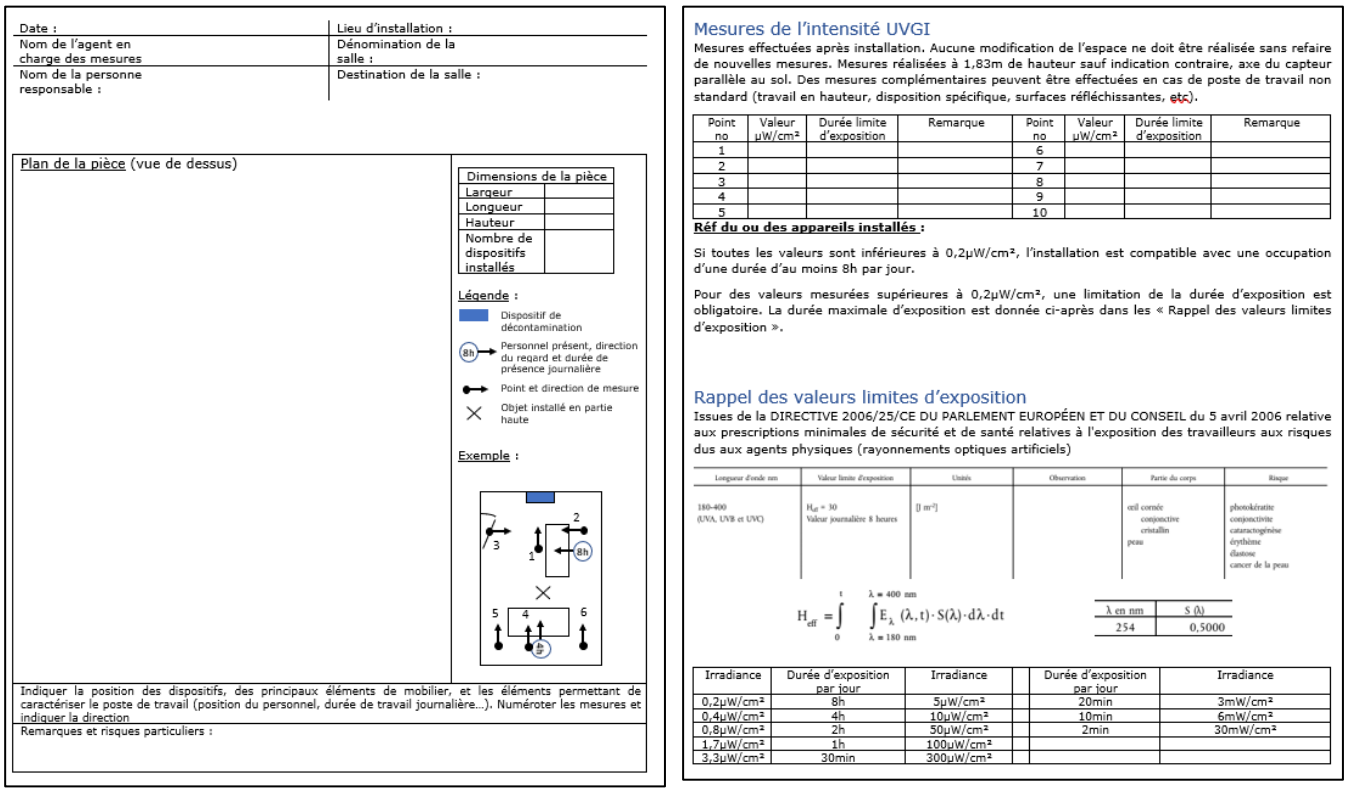
Phase 3 is used to check that decontamination equipment has been installed and is working properly.

For this phase, 2 series of measurements will be carried out:

- A series of UVGI intensity measurements in the treatment zone, to check that the germicidal intensity required for proper decontamination has been achieved (minimum 10 µW/cm^2) [38] . Measurements will be taken at various points in the treatment zone (germicidal zone), which is the area under the ceiling between 220 cm from the floor and the ceiling.
- A series of residual UVGI intensity measurements, to check that no UVC radiation is present below the germicidal zone, in order to guarantee the safety of the installation for people. These measurements will be taken at various points in the equipped room, 183cm from the floor, facing the device, in accordance with Directive 2006/25/EC of the European Parliament and of the Council of 5 April 2006 on health and safety requirements regarding the exposure of workers to the risks arising from physical agents (artificial optical radiation). The individual measurements must not exceed 0.2 µW/cm². This value of 0.2 µW/cm² is the intensity imposed by the European directive (Directive 2006/25/EC), to which a user can be exposed for 8 hours a day, without risk. By way of example, a person is exposed to an intensity of 20 µW/cm², under a May sun in Seine-et-Marne (UV8 index).

To carry out these various measurements, the equipment used will be a radio photometer with a sensitivity centered on 254nm (wavelength emitted by UVGI). This instrument will be calibrated beforehand by a certified organization such as PISEO. The radio photometer will be capable of measuring intensity levels at least ten times lower than 0.2 µW/cm².

During these measurements, the speed of air movement in the rooms will also be measured using a hot-wire anemometer (a system for measuring small air movements, of the order of 0.03 m/s), particularly at the points of entry to the treated rooms. This will enable us to identify potentially pathogen-carrying airflows from other parts of the building at the time of measurement.
This information will be recorded in documents that include room plans, names, dimensions, installation points for the device(s) and measured values (see example below).



Date :	Lieu d'installation :
Nom de l'agent en charge des mesures	Dénomination de la salle :
Nom de la personne responsable :	Destination de la salle :

Plan de la pièce (vue de dessus)

Dimensions de la pièce	
Largeur	
Longueur	
Hauteur	
Nombre de dispositifs installés	

Légende :

- Dispositif de décontamination
- 8h → Personnel présent, direction du regard et durée de présence journalière
- Point et direction de mesure
- Objet installé en partie haute

Exemple :

Indiquer la position des dispositifs, des principaux éléments de mobilier, et les éléments permettant de caractériser le poste de travail (position du personnel, durée de travail journalière…). Numéroter les mesures et indiquer la direction

Remarques et risques particuliers :

Mesures de l'intensité UVGI

Mesures effectuées après installation. Aucune modification de l'espace ne doit être réalisée sans refaire de nouvelles mesures. Mesures réalisées à 1,83m de hauteur sauf indication contraire, axe du capteur parallèle au sol. Des mesures complémentaires peuvent être effectuées en cas de poste de travail non standard (travail en hauteur, disposition spécifique, surfaces réfléchissantes, etc).

Point no	Valeur µW/cm²	Durée limite d'exposition	Remarque	Point no	Valeur µW/cm²	Durée limite d'exposition	Remarque
1				6			
2				7			
3				8			
4				9			
5				10			

Réf du ou des appareils installés :

Si toutes les valeurs sont inférieures à 0,2µW/cm², l'installation est compatible avec une occupation d'une durée d'au moins 8h par jour.

Pour des valeurs mesurées supérieures à 0,2µW/cm², une limitation de la durée d'exposition est obligatoire. La durée maximale d'exposition est donnée ci-après dans les « Rappel des valeurs limites d'exposition ».

Rappel des valeurs limites d'exposition

Issues de la DIRECTIVE 2006/25/CE DU PARLEMENT EUROPÉEN ET DU CONSEIL du 5 avril 2006 relative aux prescriptions minimales de sécurité et de santé relatives à l'exposition des travailleurs aux risques dus aux agents physiques (rayonnements optiques artificiels)

Longueur d'onde nm	Valeur limite d'exposition	Unités	Observation	Partie du corps	Risque
180-400 (UVA, UVB et UVC)	H_{eff} = 30 Valeur journalière 8 heures	[J m⁻²]		œil cornée conjonctive cristallin peau	photokératite conjonctivite cataractogénèse érythème élastose cancer de la peau

$$H_{eff} = \int_0^t \int_{\lambda=180\,nm}^{\lambda=400\,nm} E_\lambda(\lambda,t)\cdot S(\lambda)\cdot d\lambda\cdot dt$$

λ en nm	S (λ)
254	0,5000

Irradiance	Durée d'exposition par jour	Irradiance	Durée d'exposition par jour	Irradiance
0,2µW/cm²	8h	5µW/cm²	20min	3mW/cm²
0,4µW/cm²	4h	10µW/cm²	10min	6mW/cm²
0,8µW/cm²	2h	50µW/cm²	2min	30mW/cm²
1,7µW/cm²	1h	100µW/cm²		
3,3µW/cm²	30min	300µW/cm²		

Measurement setup and logging documents

Explanatory and informative sign posted in each zone equipped with a device

18.2. Microbiological procedures

Objective(s) / principles

Qualitative and semi-quantitative comparison of microbial agents present, in air and on surfaces, within areas subjected or not to UV-C (254nm) germicidal treatment using "Upper Room" type treatment devices. Samples of pathogens in the air and on test surfaces will be taken by trained technicians from the Centre Hospitalier Emile Roux biology laboratory, then analyzed by Multiplex PCR, also at the Centre Hospitalier Emile Roux biology laboratory, under the supervision of Biologist Pierre Saint Sardos

Description of venue and protocol

Within each study ENHs, 2 sampling zones will be defined in :

- an activity room
- the main dining hall

These zones will remain the same throughout the study.
In each of these zones, the following will be carried out:

- For surface sampling: on one sampling surface: 2 surfaces for bacterial sampling, one surface for viral sampling. This sampling surface will be placed on a wall, with the bottom of the sampling surfaces at 170cm from the ground.
- For air sampling: samples will be taken at a distance of 200cm from the wall bearing the decontamination device, centered on the latter and at a height of 170cm.

Materials & methods :

Surface sampling surface: self-adhesive plastic plate. Each surface in each Nursing Home will be specifically identified by a unique code to facilitate sampling
Cleaning of sampling surfaces: After installation and after each sampling operation, surfaces must be thoroughly cleaned (disinfectant wipe (30s), then cleaning wipe (30s), then isopropyl alcohol wipe (30s)).

A. Surface sampling :

- Sampling for bacterial and fungal agents :

Use of two non-selective "contact plates" based on TSA agar medium.
Each agar is applied to the surface to be tested for 10 seconds (light pressure applied by a pressure machine). Once collected, the agar plates are sent to the analysis laboratory.

- Sterile polyester-headed swabs (eSWAB) are used. During sampling, the swab is pre-moistened with the medium, then applied to the surface for 10 seconds, rubbing horizontally, then vertically, then diagonally. The swab is then placed in the tube containing the medium and stored at 4°C until dispatched to the laboratory for inoculation on agar plates.

For each bacterial sample, samples will be taken in duplicate.

- Sampling viral agents :

Sterile polyester-headed swabs are used in conjunction with UTM medium for viral preservation. During sampling, the swab is pre-moistened with UTM medium, then applied to the surface for 10 seconds, rubbing horizontally, then vertically, then diagonally. The swab is then placed in the tube containing the UTM medium and stored at 4°C until dispatched to the laboratory for storage at -80°C until analysis.

Summary:

Withdrawals	Media considered	Sampling equipment	Location of sampling areas by ENH	Sampling frequencies and Opening hours

Surface	Bacterial sampling	- 2 x "Contact box" Columbia medium - 2 eSWAB swabs	- refector principal - activity room	Once every 7 weeks at the same time (after lunch)
	Viral sampling	2 sterile polyester-headed swabs		

B. Air sampling :

The protocol adapted from Gendron *et al* [65] will be used for sampling.

- PTFE (polytetrafluoroethylene) filter connected to a 20l/min flow-controlled pump for 20 min. The filter is then stored at 4°C until dispatched to the laboratory for conditioning.
- In the laboratory, the TSB tube containing the filter will be vortexed for 20 min at maximum speed, and the TSB medium divided into 3 aliquots: 1 aliquot seeded as soon as possible on agar media comparable to those used for surface sampling (see above) and 2 aliquots stored at -80°C for viral testing (1 aliquot) and subsequent analysis if required.

Summary:

Withdrawals	Support considered	Sampling equipment	Location of sampling areas by ENH	Sampling frequencies and Opening hours
Air	Air in the sampling zone	Air sampler	- refector principal - activity room	1 time every 7 weeks at the same time

C. Detection and identification of microbial agents

- Bacterial and fungal cultures :

Agar plates (TSA agar contact plates) are incubated for 7 days at 35°±2°C in a controlled atmosphere containing 5% CO_2. Microbial growth and enumeration will be assessed after 1, 2, 5 and 7 days of incubation.

- Bacterial and fungal identification :

Microbial colonies found in culture will be identified by MALDI-TOF-MS (Matrix Assisted Laser Desorption Ionisation/Time Of Flight) mass spectrometry (Bruker, Daltonic). Fungi, excluding yeasts, can be identified by light microscopy if required.

- Detection of viral agents :

The presence of COVID-19, Influenza A and B viruses (influenza A and influenza B) and respiratory syncytial virus (RSV) will be tested by PCR using the Triplex Thermo Fisher TaqPath COVID-19, FluA/B, RSV Combo Kit (ref A49867).