Efficacy of Ultraviolet Germicidal Irradiation (UVGI) Devices to Decrease the Incidence of Respiratory Infections in Nursing Homes: a Cluster Randomized Crossover Trial

(RESPROTECT)

STATISTICAL ANALYSIS PLAN Part 1 (clinical endpoints)	**Version**	
	3.0	29/04/2026

STUDY INFORMATION	
Sponsor	Centre Hospitalier Emile Roux, Le Puy en Velay, France
Funding Agency	ANRS-MIE
Protocol Number	V3.0, dated 23/09/2025
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VERSIONS		
Version	**Date**	**Main edits**
1.0	**16/07/2025**	**-**
2.0	**30/09/2025**	**Former first secondary endpoint becomes primary endpoint** **Former primary endpoint becomes first secondary endpoint**
3.0	**29/04/2026**	**Clarification regarding multiple testing.** *This last amendment to the statistical analysis plan was adopted before the analysis was carried out.*

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MAIN ABBREVIATIONS

ARI: Acute Respiratory Infection

AEI: Adverse event of interest

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

UVGI: Ultraviolet Germicidal Irradiation

1 SUMMARY OF THE PROTOCOL

Ref: RESPROTECT protol V3.0.

1.1 Study design

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

1.2 Intervention

The intervention assessed consists of UVGI devices installed in the common living areas of 12 nursing homes. All devices are turned on at baseline. Some devices are deactivated by installing an invisible internal filter. Deactivation filters are installed by a team independent of the investigation team. Deactivation is therefore carried out blind to patients, caregivers and the investigation team.

1.2.1 Intervention

The UVGI devices are unfiltered (active).

1.2.2 Placebo

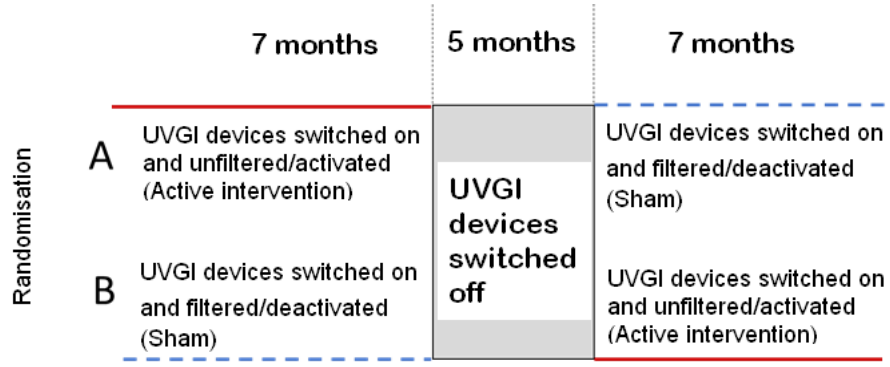
The UVGI devices are filtered (inactive sham).

1.3 Randomisation

Participating nursing homes are randomised into two arms, A and B, in a 1:1 ratio.

- In arm A: UVGI devices are unfiltered/active during period 1, and filtered/inactivated during period 2.
- In arm B: UVGI devices are filtered/inactivated during period 1 and unfiltered/active during period 2.

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



1.4 Objectives and endpoints

Objectives	Endpoints
Primary	
To compare the incidence of severe* acute upper and lower respiratory infections† between periods when UVGI devices are active and periods when UVGI devices are inactive	Severe* symptomatic upper and lower respiratory infections†.

Objectives	Endpoints
Secondary	
1. To compare the incidence of acute respiratory infections, all grade of severity combined, between periods when UVGI devices are active/inactive	1. Symptomatic upper and lower respiratory infections, all grade of severity combined,
2. To compare the incidence of all-cause hospitalization or death between periods when UVGI devices are active/inactive	2.1 All-cause hospital admission 2.2 All-cause death 2.3 All cause hospital admission or death
3. To compare the incidence of adverse events of interest††, overall and by severity grade between periods when UVGI devices are active/inactive	3. Non-infectious adverse events of interest††, overall and by severity grade (CTCAE classification).
4. To compare the consumption of antibiotics between periods when UVGI devices are active/inactive	4. Quantity of anti-infectives used, overall and by class
5. To compare the presence of pathogens in the air and on test surfaces between periods when UVGI devices are active/inactive	5.1 Viral load and bacterial load in air samples collected in common living areas 5.2 Viral load and bacterial load on fomite sampling in common living areas
6 To measure the medico-economic benefits of equipping patients with UVGI systems	6. Incremental Cost-Effectiveness Ratio

* Severe acute respiratory infection = acute respiratory infection requiring oxygen therapy, or followed by hospitalization or death within 30 days, regardless of the cause

† Upper ARI: sinusitis, otitis media, nasopharyngitis, angina; Lower ARI: tracheitis, bronchitis, pneumonia, pulmonary abscesses and COPD exacerbations ; Symptomatic infection with SARS-Cov-2, influenza virus or respiratory syncytial virus will be considered by default as a lower respiratory infection, even if extra-respiratory symptoms predominate.

†† keratitis and erythematous skin eruptions occurring in light-exposed areas.

1.5 Population

Center eligibility criteria

Inclusion criteria:

Nursing Homes:

- Having a system 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 provide all residents or their legal guardians/curators with an individual information leaflet.

Exclusion criteria:

Nursing Homes:

- Already equipped with another air treatment system in common living spaces.
- Not wishing to be equipped with UVGI devices in all rooms considered necessary to be equipped according to the trial coordinating investigator.
- Having planned a major change to the structure (extension, renovation, closure, requalification, etc.) during the course of the study, which could affect the study population and/or UVGI air treatment devices.

Individual eligibility criteria

Inclusion criteria:

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) are eligible.

Exclusion criteria:

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 are not included.

1.6 Sample size calculation

Each cluster has an approximate size of 90 participants with a low coefficient of variation. It is estimated that 80% of participants will be present during both periods. As those who die or leave the center are replaced, the number of participants remains constant throughout the study. The intra-cluster coefficient of variation (WP-ICC ρ) is estimated at 0.1 (10% of respiratory infections are explained by the nursing home environment). The inter-period correlation (inter-period ICC η) is estimated to be negligible (the two periods are in the same calendar period one year apart). The cluster autocorrelation (CAC) is set at 0.5 (i.e. $\eta = 0.05$), a number recommended when assumptions are limited (4). The individual autocorrelation (IAC) is set at 0.2. Assuming an incidence of acute respiratory infections of 17 per 100 patient-years when UVGI devices are inactivated, it is estimated that 12 Nursing Homes need to be included to demonstrate at least a 50% reduction in the incidence of ARI, with a two-sided alpha risk of 0.05 and a power of 80% (5,6).

2 STATISTICAL ANALYSIS

2.1 Definitions

2.1.1 Study period

Period 1 starts on October 1st, 2024 and ends on April 30, 2025.

Period 2 starts on October 1st, 2025 and ends on April 30, 2026.

2.1.2 Baseline

There are two baseline dates, one for period 1 and one for period 2.

Each participant has their own baseline date for each period.

The date of baseline is:

- For period 1:
  - October 1, 2024, if the participant was already present on October 1st, 2024.
  - The date of entry to the Nursing Home if the participant arrived at the Nursing Home between October 2, 2024, and April 30, 2025.
- For period 2:
  - October 1, 2025, if the participant was already present on October 1st, 2025.

- The date of entry to the Nursing Home if the participant arrived at the Nursing Home between October 2, 2025, and April 30, 2026.

2.1.3 End of follow-up

There are two end-of-follow-up dates, one for period 1 and one for period 2.

Each participant has their own end-of-follow-up date for each period.

- For period 1, the end of follow-up of a participant is April 30, 2025 or the date of *premature end of follow-up** in period 1.
- For period 2, the end of follow-up of a participant is April 30, 2026 or the date of *premature end of follow-up** in period 2.

* Premature end of follow-up = death, OR [transfer to another nursing home, return to home or transfer to another care facility] AND no return to the nursing home before the end of the period.

  - A participants included in a given Nursing Home who is transferred to another Nursing Home during the study is considered to have withdrawn from the study. If the new Nursing Home participates in the study, he/she is re-included as a new participant at his/her new Nursing Home, with a new study ID code. The list of participants who participated with two different ID codes in two different Nursing Homes is shown in the final report.

2.1.4 Individual follow-up time

Each participant has two follow-up times:

- Period 1 follow-up time is the time the participant is present in the Nursing Home between baseline 1 and April 30, 2025 or the date of premature end of follow-up in period 1. The time of discontinuation of the intervention* in period 1 is deducted from the follow-up time.
- Period 2 follow-up time is the time the participant is present in the Nursing Home between baseline 2 and April 30, 2026 or the date of premature end of follow-up in period 2. The time of discontinuation of the intervention* in period 2 is deducted from the follow-up time.

* Discontinuation of the intervention = transfer to another nursing home, return to home or transfer to another care facility) AND return to the nursing home before the end of the period

2.1.5 Prevalent and incident ARI

- Incident ARI are ARI episodes starting >7 days after baseline.
- Prevalent ARI are ARI episodes starting $\leq$ 7 days after baseline.

2.1.6 Severe ARI

Severe ARI = ARI requiring oxygen therapy, or followed by hospitalization or death within 30 days, regardless of the cause

2.1.1 Hospitalization

Hospitalization = unscheduled admission to a hospital ward or a visit to the emergency room, even if that visit does not result in admission. Scheduled hospitalizations are not included in the analysis.

2.1.2 Protocol deviations

A list of all protocol deviations is shown in the final report.

2.1.1 Opt-out

Residents in participating Nursing Homes or their relatives may refuse the analysis of their personal data. Data from individuals opting out are deleted from the database. The number of individuals opting out is shown in the final report.

2.2 Statistical principles

2.2.1 Level of statistical significance

We will use a two-sided type I error α of 5% to compare endpoints between study groups.

2.2.2 Description and comparison

Categorical variables will be described in terms of frequency and percentage per category. 95% confidence intervals will always be reported. When the number of categories is >2, a dichotomized categorization may also be shown based on the distribution or on the clinical significance. Comparison will use χ^2, Fisher's exact test or any other appropriate test, depending on the observed frequencies.

Continuous variables will be described in terms of absolute frequency, mean, standard deviation and standard error, or median, interquartile range and range, depending on the variable distribution. Data may be transformed and normalized whenever necessary. Comparison will use Student's t test, Kruskal-Wallis test or Wilcoxon test or any other appropriate test, depending on the distribution of the variable.

Time-to-event variables will be described in terms of incidence per 100 person-years and probability of occurrence at different timepoints using the Kaplan-Meier method. Comparison will use log-rank test or Cox proportional hazards models.

2.2.3 Covariate adjustment

Comparisons between groups will be systematically performed:

- Adjusted for baseline characteristics in the main analysis. Baseline characateristics considered in the adjustment will be: sex, baseline age for period 1, baseline age for period 2, baseline GIR score for period 1, and baseline GIR score for period 2.
- Unajusted for baseline characteristics (crude) in sensitivity analysis.

A posteriori adjustment may be made for other variables identified as potential confounders.

2.2.4 Multiple testing

- The main hypothesis of the trial is that, in the elderly population or nursing homes, UVGI could reduce the incidence of ARI of all grades, and therefore also reduce the incidence of severe ARI, ARI-related hospitalizations and ARI-related deaths. Reducing the incidence of ARI-related hospitalizations and ARI-related deaths would likely decrease the all-cause hospitalization rate and all-cause mortality, as ARI is believed to be a leading cause of hospitalization and death in this population during the winter months.
- Four outcomes will test the trial main hypothesis : "severe IRA" (primary outcome), "IRA of all grades" (secondary outcome), "all-cause mortality" (secondary outcome) and " all-cause hospitalization" (secondary outcome).
  - The four outcomes are clinically relevant, and a reduction in their incidence has the potential to be interpreted as an indication of UVGI effectiveness.
  - The four are interdependent : should UVGI has an effect, they would likely all vary in the same direction.
  - "Severe acute respiratory infection" was chosen as the primary outcome because it has the potential to be the most clinically compelling target for the intervention. However, it is a soft outcome that depends on observation by staff in non-healthcare settings where transient respiratory disturbances can be difficult to interpret in elderly individuals with multiple comorbidities. Even though their reporting is based on standardized criteria, the is a risk of underestimation (ARI wrongly interpreted as a non-infectious episode) or overestimation (non-infectious episode wrongly interpreted as an ARI). There is no indicator that would allow to measure the phenomenon of overestimation or underestimation in a given investigating center, and to adjust the analysis for a possible imbalance between intervention groups.

- All-cause mortality and all-cause hospitalization are less specific to the intervention, but are hard outcomes: they are objective and their completeness is easy to obtain by cross-referencing the trial database with the administrative records of the investigation centers.

To account for the risk of Type 1 error linked to multiple testing :

- We will not adjust for multiple testing for these 4 outcomes, because they are expected to be highly correlated and alpha-adjustment for multiple comparisons may increase the chances of a Type 2 error. However, we will interpret and discuss jointly the results of the analysis for these four outcomes according to their consistency. If the analysis reaches statistical significance for some criteria but not for others, and if the non-significant results do not show the same trend as the significant results, the interpretation should be nuanced and this discrepancy should be explained. This is particularly true if the primary outcome measure is inconsistent with the others.
- We will limit comparisons between groups to these four outcomes. Analyses of other secondary outcomes, as well as all sensitivity analyses will be considered exploratory. For all exploratory analyses, we will not report p values : we will only present effect estimates with 95% confidence intervals, specifying that the widths of these intervals have not been adjusted to account for multiple testing and should not be used to conclude statistical significance.

2.2.5 Statistical software

We will use SAS® software (version 9.4 or higher) or R software versions 4.2.2 or higher to conduct statistical analyses.

2.2.6 Calculation of time between two dates

- Time between two dates in month = (Date2 dd/mm/yyyy – Date1 dd/mm/yyyy) / 30.4375
- Time between two dates in year = (Date2 dd/mm/yyyy – Date1 dd/mm/yyyy) / 365.25
- Age at baseline in year = (Inclusion date dd/mm/yyyy – Birth date 15/mm/yyyy) / 365.25

2.2.7 Missing birth dates

- When the year is missing, no imputation will be done.
- When the year is recorded but the month is missing, missing months will be imputed to July.

2.2.8 Other missing data

General strategy

Missing data distribution (number and proportion) will be described. Further investigation will be conducted to document the nature of missingness.

Missing data on covariates

For explanatory variables missing for less than 10% of participants, multiple imputation could be proposed, provided that the assumption of the random nature of the loss of information is verified.

For explanatory variables missing for more than 10% of residents, no imputation will be performed.

2.3 Analysis plan

2.3.1 Protocol deviations

A list of all protocol deviations will be provided.

2.3.2 Characteristics of the centers

The following Nursing Home characteristics will be presented by study arm (A & B), by period (1 & 2) by intervention group (active vs placebo) and by Nursing Home (separating period 1 and 2)

- Number of beds open during the study periods (in bed-days).

- Number of staff working in the Nursing Home during the study periods, overall and by category (in FTE – full-time employee equivalence).
- Consumption of antibiotics, overall, by class and by molecule: daily doses per 100 days of follow-up.
- Number of UCGI devices.
- Number of UCGI devices suspected of being inapropriately used during the study periods.

2.3.3 Baseline and follow-up characteristics pf the participants

The following participant characteristics will be presented by study arm (A & B), by period (1 & 2) by intervention group (active vs placebo) and by center (separating period 1 and 2)

	Variable	Continuous	Categorical
Flow chart	**Individuals present in the Nursing Home at any time**	-	3 categories: included, opting-out, non-included for other reasons
	Included patients (N)	-	Overall and 3 categories: present during the 2 periods, present only during period 1, present only during period 2
BASELINE ǂ	**Sex**	-	n/N (%) 2 categories: Male, Female
	Age (years)	Distrib.	n/N (%) 4 categories: <65; 65-74; 75-84; ≥85
	BMI (Kg/m2)	Distrib.	n/N (%) 4 categories: <18; 18-24; 25-29; ≥30
	Accommodation	-	n/N (%) 4 categories: Cantou, USLD, EHPAD, NC
	Mobility	-	n/N (%) 3 categories: ambulant, wheelchair, bedridden
	GIR index	Distrib.	n/N (%) 7 categories: 1, 2, 3, 4, 5, 6, NC
	Number of comorbidities	Distrib.	-
	Charlson comorbidity index	Distrib.	n/N (%) 4 categories: 0 ; 1-2 ; 3-4 ; ≥5
	Vaccinations :		
	Influenza, ever vaccinated prior to baseline	-	n/N (%) 4 categories: No, Yes ≤6 months, Yes >6 months, NC
	If yes, time since last vaccination (months)	Distrib.	-
	Covid19, ever vaccinated prior to baseline	-	n/N (%) 4 categories: No, Yes ≤6 months, Yes >6 months, NC
	If yes, time since last vaccination (months)	Distrib.	-
	Pneumococcus, ever vaccinated prior to baseline	-	n/N (%) 3 categories: No, Yes, NC
	If yes, time since last vaccination (months)	Distrib.	-
	Pertussis, ever vaccinated prior to baseline	-	n/N (%) 3 categories: No, Yes, NC
	If yes, time since last vaccination (months)	Distrib	-
FOLLOW-UP #	**Follow-up time, per participant (months)**	Distrib.	-
	Cumulative follow-up time	p-years	-
	Status at the end of period 1	-	n/N (%) 3 categories: alive and still present, dead, other premature end
	If other premature end, detail	-	n/N (%) 2 categories: transfer to another facility, definitive return to home
	Vaccination status		
	Influenza, ever vaccinated*	-	No, Yes, NC
	Covid19, ever vaccinated*	-	No, Yes, NC
	Pneumococcus, ever vaccinated*	-	No, Yes, NC
	Pertussis, ever vaccinated*	-	No, Yes, NC

* Including vaccination prior to baseline and new vaccination between baseline and end of period

ǂ « Baseline » will be described in 2 steps : (i) Description of all participants upon their inclusion in the study, regardless of whether this inclusion took place in the 1st or 2nd period : this concerns all variables ; (ii) Separate description of participants included in period 1 and those who participated in period 2 (whether or not they had already participated in period 1): this only concerns the variables sex, age, BMI, GIR score and those related to vaccination.

« Follow-up » will be described separately for period 1 and period 2 ;

2.3.1 Characteristics of events

The events recorded during follow-up are ARIs, AEIs, all-cause hospitalisations and all-cause deaths.

The following characteristics of events will be presented:

- For all events: by study arm (A & B), by period (1 & 2) by intervention (active vs placebo) and by center (separating period 1 and 2).
- For ARIs only: by type of events (prevalent/incident).

Variable	Continuous	Categorical
ALL ARIs	-	
Total number of ARIs	-	N0
Total number of incident ARIs		N1
Incident ARI description :		
Clinical type	-	n/N1 (%) 2 categories: Upper/Lower
Higher ARI, diagnosis	-	n/N1 (%) 3 categories: sinusitis, rhinopharyngitis, laryngitis
Lower ARI, diagnosis	-	n/N1 (%) 3 categories: bronchitis, pneumonia, others
Reported impaired swallowing < 72h	-	n/N1 (%) 3 categories: Yes/No/NC
Microbiological type	-	n/N1 (%) 4 categories: bacterial, viral, other, NC
If viral, detail	-	n/N1 (%) 4 categories: Covid19, Influenza, SRV, other
Radiology exam	-	n/N1 (%) 3 categories: Yes/No/NC
If yes, result	-	n/N1 (%) 3 categories: Normal/abnormal/NC
CRP measured	-	n/N1 (%) 3 categories: Yes/No/NC
If yes: time since 1st symptoms (days)	Distrib.	-
If yes: value (mg/L)	Distrib.	-
Severity		
ARI *leading to* 02 therapy, hospitalisation or death	-	n/N1 (%)
Combination of severity criteria	-	n/N1 (%) Pivot table 3x3: Oxygen/hospi/death (with row and column totals)
ARI with antibiotherapy	-	n/N1 (%) 3 categories: Yes/No/NC
Duration:		
Per episode of ARI with antibiotherapy	Distrib.	
Per participant n1 (day/person)	Distrib.	
Per participant N (day/person)	Distrib.	-
Cumulative among N (days)	N o days	-
ARI with antiviral treatment	-	n/N1 (%) 3 categories: Yes/No/NC
If yes, duration per episode of antiviral treatment	Distrib.	-
ARI with oxygen therapy	-	n/N1 (%)
Duration :		
per episode with oxygene therapy	Distrib.	

per participant n1 (day/person)	Distrib.	
per participant N (day/person)	Distrib.	-
Cumulative among N (days)	N o days	-
Favorable evolution at day 5	-	n/N1 (%) 3 categories: Yes/No/NC
Favorable evolution at day 10	-	n/N1 (%) 3 categories: Yes/No/NC
FIRST incident ARI		*(N=number of included participants)*
Participants with at least one episode of:	-	
ARI		n/N (%)
ARI with antibacterial treatment	-	n/N (%)
ARI with antiviral treatment		n/N (%)
ARI with Oxygen therapy	-	n/N (%)
ARI *with* hospitalisation within 30 days	-	n/N (%)
ARI *leading to* hospitalisation within 30 days		n/N (%)
ARI *with* death within 30 days	-	n/N (%)
ARI *leading to* death within 30 days		n/N (%)
Severe ARI (*leading to* O2, hospi or death)	-	n/N (%)
ALL AEI		
Number of AEI :		
Overall	-	N2
By diagnosis	-	3 categories: keratitis, erythema, other
By severity grade	-	n/N2 (%) 3 categories: CTCAE 1 to 5, NC
By causality	-	n/N2 (%) 4 categories: no, possible, probable, NC
Leading to hospitalisation	-	n/N2 (%) 3 categories: yes, no, NC
FIRST AEI		
Participants with at least one episode of AEI (n2)	-	n/N (%)
DEATH		
Total number of deaths (N3)		n/N (%)
Cause	-	n/N3, 2 categories: ARI, Other
If other	-	List
Place of death	-	n/N3, 3 categories: At hospital, at Nursing Home, other

Variable	Continuous	Categorical
ALL HOSPITALIZATION*	-	
Total number of hospital admissions	-	N4
Cause	-	n/N4 (%), 2 categories: ARI/Other
If other	-	List
Duration of hospital stay:		
Per episode N4	Distrib.	
Per participant n4 (day/ person)	Distrib.	
Per participant N (day/person)	Distrib.	
Cumulative among N (days)	N of days	-
Issue	-	n/N4 (%) 3 categories: Death, return to Nursing Home, other
FIRST HOSPITALIZATION*		
Participants with at least one episode of:	-	
Hospital admission (n4)	-	n/N (%)
ARI-related hospital admission	-	n/N (%)
Non-ARI-related hospital admis.	-	n/N (%)
OUTCOMES		
Incidence and KM Probability of first ARI		
Incidence and KM Probability of first severe ARI		
Incidence and KM Probability of first AEI		
Incidence and KM Probability of first severe AEI		
Incidence and KM Probability of all-cause death		
Incidence and KM Probability of first all-cause hospital admission		
Incidence and KM Probability of first all-cause hospital admission or all-cause death		

* In the primary analysis of the "hospitalization" and "hospitalization or death" endpoints, pre-planned hospital admissions (e.g., for chronic conditions or corrective surgery) will be excluded from the analysis. They will be included in a sensitivity analysis of these endpoints.

2.4 Primary endpoint

2.4.1 Main analysis

The primary endpoint is the incidence of first severe ARI (see definition in section 2.1.6).

Incidence will be compared between periods when UVGI devices are active and periods when UVGI devices are inactive.

- The numerator will be the number of people who experienced at least one incident (see definition in section 2.1.6) severe ARI during a period.
- The denominator will be sum of the follow-up time without incident severe IRA of all participants. A participant follow-up time without severe IRA is the time between baseline and the date of the first incident severe IRA (if any) or the date of end-of follow-up in the period. The time of discontinuation of the intervention (definition above) before the occurrence of the first IRA (if any) or before the end-of follow-up in the period is deducted from the follow-up time.

In first intention :

Analysis will be carried out at the individual level, using a generalised linear mixed model (GLMM) with:

- a Poisson distribution or a negative binomial distribution in the event of overdispersion as the outcome is incidence. In practice with SAS, we will replace dist=poisson by dist=nb (Negative binomial) in case of surdispersion (if the observed variance exceeds the mean);

- a logarithmic link function;

- an offset term for the number of patient-years;

- fixed effects:

  - study arm intervention,
  - period,
  - baseline characteristics: sex, baseline age for period 1, baseline age for period 2, baseline GIR score for period 1, baseline GIR score for period 2.

- random effects:

  - at the level of clusters,
  - cluster-periods,
  - clusters-individuals;

The correlation structure will be of the exchangeable block type (coded in SAS type=cs).

The intervention effect will be expressed as an incidence rate ratio (IRR) (with a 95% CI), between the intervention and the placebo/sham.

The Kenward-Rodger correction(9) will be applied to estimate the number of degrees of freedom as it has been shown to improve estimation with a small number of clusters (10–12).

The following parameters will be reported:

- The intra-cluster coefficient of variation (WP-ICC, ρ) that is the correlation between two outcomes from the same cluster-period.
- The inter-period correlation (between-period ICC, η) that is the correlation between two outcomes from the same cluster but different periods.
- The cluster auto-correlation (CAC) = η / ρ
- The individual auto-correlation (IAC) that represents the within-individual dependencies over time.

In second intention:

- If the individual-level model does not converge due to low numbers of clusters, we will carry on a cluster-level analysis (13) ;
- If the model adjusted for baseline characteristics does not converge or if the random effect estimates become unstable (variance ≈ 0 or standard errors > 2× those of the unadjusted model), we will use an unadjusted mixed Poisson model.

2.4.2 Sensitivity analyses

Sensitivity analyses will be performed:

- By defining « severe ARI » as an ARI requiring oxygen therapy, or followed by hospitalization or death within 30 days AND for which the ARI was considered responsible for hospitalization or death.
- By defining « severe ARI » as an ARI requiring oxygen therapy lasting >1 day, or followed by hospitalization or death within 30 days, regardless of the cause
- By defining « severe ARI » as an ARI requiring oxygen therapy, or followed by hospitalization lasting >1 day (ie : excluding emergency visits without further hospital admission) or death within 30 days, regardless of the cause
- By defining incident ARI as ARI episodes starting: (i) >4 days after baseline; (ii) the day after baseline or later.
- By excluding hospitalisation and/or deaths occuring ≤ 7 days after baseline
- Using a crude model (unadjusted for baseline characteristics)
- Using the cumulative incidence of severe IRA as the endpoint, with the total number of severe IRA as the numerator and the sum of individual follow-up times as denominator.

2.4.3 Exploratory Subgroup analyses

The analysis will be stratified between participants housed in Memory Support Units (MSUs) and others.

Other clinically relevant subgroup analyses may be proposed after studying the subgroup × arm interaction in the above regression models.

2.5 Clinical secondary endpoints

Clinical secondary endpoints are the following:

- Incidence of ARIs of any grade.
- Incidence of all-cause hospitalisation, all-cause death, and all causes ‘hospitalisation or death’ including all hospitalisation and/or deaths, regardless of the time elapsed since baseline and (for hospitalisations) regardless of their duration.
- Incidence of non-infectious AEIs, overall and by severity grade (CTCAE classification).

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.

Sensitivity analyses will be performed:

- Including only hospitalisation and/or deaths occuring >7 days after baseline.
- Including only hospitalization lasting >1 day

2.6 Other secondary endpoints

Other secondary endpoints are the following:

- Quantity of antibiotics used, expressed as days of therapy (DOT).

- Microbiological loads in air and fomite samples, expressed as cycle threshold (Ct) values and number of genome copies/m³ for viral agents; and colony-forming units (CFU)/cm² for bacterial and fungal agents.

Outcomes will be compared using mixed-effects linear regression models, including random effects for cluster and period. The result will be expressed as the mean difference (with a 95% CI) between the intervention and the placebo.

The analysis of the economical secondary endpoint will be detailed in a separate protocol.

2.7 Interim analyses

No interim analysis is planned. The DSMB 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 interim analysis is performed for efficacy, the Haybittle-Peto stopping rule will be used: p-value=0.0027. As this rule is conservative, the significance level would remain at α=5% for the final analysis.

3 REFERENCES

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