

**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		Version
Part 1 (clinical endpoints)	2.0	30/09/2025

STUDY INFORMATION	
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VERSIONS		
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1.0	16/07/2025	-
2.0	30/09/2025	Former first secondary endpoint becomes primary endpoint Former primary endpoint becomes first secondary endpoint

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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

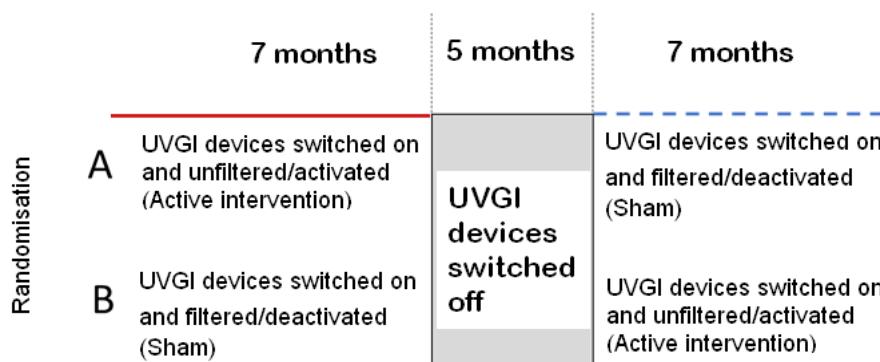
The UVGI devices are filtered (inactive sham).

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
<i>Primary</i>	
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
<i>Secondary</i>	
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 = leading to oxygen therapy, hospitalisation or death

† sinusitis, otitis media, nasopharyngitis, angina.

†† tracheitis, bronchitis, pneumonia, pulmonary abscesses and COPD exacerbations. Symptomatic infection with SARS-CoV-2 will be considered by default as a 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 participant 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 >5 days after baseline.
- Prevalent ARI are ARI episodes starting ≤ 5 days after baseline.

2.1.6 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 conducted:

- Unadjusted;
- adjusted on the following 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.

A posteriori adjustment could be conducted for other variables identified as potential confounding factors.

2.2.4 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.

2.2.5 Calculation of time between two dates

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

2.2.6 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.

2.2.7 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.

- Consumption of hydroalcoholic gel: volume of hydroalcoholic gel used per 100 days of follow-up.
- Consumption of personal protective equipment: number of personal protective equipments used per 100 days of follow-up.
- Number of UCGI devices.
- Number of UCGI devices suspected of being inappropriately used during the study periods.
- Respiratory virus epidemic in the center in the month preceding the start of the period.

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	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.	
	Vaccinations :		
	Influenza, ever vaccinated prior to baseline	-	n/N (%) 4 categories: No, Yes ≤6 months, Yes >6 months, NC
FOLLOW-UP	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 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 prior vaccination and new vaccination between baseline and end of period

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
ARI	FIRST ARI		
	Participants with at least one episode of:	-	
	ARI (n1)		n/N (%)
	Upper ARI	-	n/N (%)
	Lower ARI	-	n/N (%)
	ARI with antibiotherapy	-	n/N (%)
	ARI with Oxygen therapy	-	n/N (%)
	ARI with hospitalisation within 30 days	-	n/N (%)
	ARI with death within 30 days	-	n/N (%)
	Severe ARI (O2, hospi or death)	-	n/N (%)
	ALL ARIs	-	
	Total number of ARIs	-	N1 , overall, and 2 categories: Prevalent/Incident
	ARI types	-	n/N1 (%) 2 categories: Upper/Lower
	Higher ARI, diagnosis	-	n/N1 (%) 3 categories: sinusitis, rhinopharyngitis, laryngitis
	Lower ARI, diagnosis	-	n/N1 (%) 4 categories: bronchitis, pneumonia, pulmon.abscess, COPD ex.
	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 with oxygen therapy, hospitalisation or death	-	n/N1 (%)
	Combination of severity criteria	-	n/N1 (%) Pivot table 3x3: Oxygen/hospi/death (with row and column totals)
	Antibacterial treatment	-	-
	ARI with antibiotherapy	-	n/N1 (%) 3 categories: Yes/No/NC

	Variable	Continuous	Categorical
AEI	Duration:		
	Per episode of ARI with antibiotherapy	Distrib.	
	Per participant n1 (day/person)	Distrib.	
	Per participant N (day/person)	Distrib.	-
	Cumulative among N (days)	No days	-
	Antiviral treatment	-	n/N1 (%) 3 categories: Yes/No/NC
	If yes, duration per episode of antiviral treatment	Distrib.	-
	Oxygen therapy		
	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)	No days	-
All cause death	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 AEI		
	Participants with at least one episode of AEI (n2)	-	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
	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 cause hospital admission	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 (%)
	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
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		

2.4 Primary endpoint

2.4.1 Main analysis

The primary endpoint is the incidence of first severe ARI (severe = leading to oxygen therapy, or followed by hospitalisation within 30 days or death within 30 days).

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 (definition above) severe IRA 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,

- random effects:

- at the level of clusters,
- cluster-periods,
- clusters-individuals;
- and 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-Roger 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, in case the model does not converge due to low numbers of clusters, we will use the cluster-level analysis (13)(p197).

2.4.2 Sensitivity analyses

Sensitivity analyses will be performed:

- By defining incident severe IRA as severe ARI episodes starting: (i) >7 days after baseline; (ii) the day after baseline or later.
- By adjusting the model for the following variables: gender, age and GIR index. The latter two variables will be measured at the beginning of each period;
- 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. The model will be the same as the model used in primary analysis, with the addition of a random individual-period effect; The models will be the same as that used in primary analysis.

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 \times 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’.
- 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.

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 $\alpha=5\%$ for the final analysis.

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