



Statistical Analysis Plan (SAP)

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FAMILIFE

Evaluation of the experiences of relatives of patients hospitalized in palliative care units.

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History of changes

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Protocol version

The protocol version use is V2 since 12 february 2018.

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List of abbreviations and definition of terms

ABREVIATION	DEFINITION
HADS	Hospital Anxiety and Depression Scale
ICH	International Council for Harmonization
IGC	Inventory Complicated Grieg
ITT	Intent To Treat
ITTS	Intent To Treat Set
PP	Per Protocol
PPS	Per Protocol Set
PTSD	Syndrome de Stress Post-Traumatique
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
PCU	Palliative Care Units
D	Day

1 - Introduction

Statistical methodology which describes specifications, tables, figures and statistical programming lists to be used is stored in the Statistical Analysis Plan (SAP). It describes exploratory variables and populations, predicted data transformations and manipulations, and other analytical details not provided in the study protocol.

The analyzes described are based on the V2 clinical study protocol of February 12, 2018 and will be prepared in accordance with Directive E9 of the International Council for Harmonization (ICH).

Statistical analyzes will be carried out by ICUREsearch's biostatistics unit in agreement with the sponsor.

The PAS will be validated and signed before database lock.

2 - Objectives

2.1 Primary endpoint

PRIMARY ENDPOINT	MAIN CRITERION
Measurement of the incidence and risk factors of prolonged grief in families 6 months after date of death. Prolonged grief in families 6 month after death day, incidence, and risk factor measurement.	A score >25 of the Inventory Complicated Grief (IGC) questionnaire defines prolonged grief.

Justification:

Few studies in France have evaluated these consequences in the families of patients who died in palliative care units (PCUs).

2.2 Secondary endpoints

SECONDARY ENDPOINTS	SECONDARY CRITERIA
1. Measurement of the anxiety and depression score of families between D3 and D5 of admission in the USP	Score >8 of the Hospital Anxiety and Depression Scale (HADS) questionnaire defining symptoms of anxiety and severe depression
2. Measurement of the anxiety and depression score of families 6 months from the date of death	Score >8 of the Hospital Anxiety and Depression Scale (HADS) questionnaire defining symptoms of anxiety and severe depression
3. Determinants of the change in the anxiety and depression score of families between D3 and D5 of admission and 6 months from the date of death	Score >8 of the Hospital Anxiety and Depression Scale (HADS) questionnaire defining symptoms of anxiety and severe depression
4. Measurement of the incidence of post-traumatic stress disorder (PTSD) in families 6 months from the date of death and measurement of risk factors for PTSD	Score >22 of the Impact of Event Scale-Revised questionnaire defining symptoms of post-traumatic stress disorder

SECONDARY ENDPOINTS	SECONDARY CRITERIA
5. The bereavement experience will be explored by a qualitative analysis including families with an IGC score >25	Phenomenological interpretative analysis of the interviews carried out with bereaved families with an IGC > 25. The interviews are recorded, transcription of verbatim. The analysis will be done with two psychologists to determine how the bereaved describe the prolonged grief and to highlight the measures of help to be provided.

2.3 Hypothesis

Patient quantity-based hypothesis:

We assume that we have 25% prolonged grief. Longitudinal family surveillance studies show that 40% are lost to follow-up at 6 months. A total of 500 patients included and 450 potentially included families will detect risk factors for pathological bereavement with OR value of 2 with an alpha risk value of 0.05 and a beta risk value of 0.2 (assuming the independence of prolonged grief of the members from the same family). Beds numbers will constraint patient inclusion (17 inclusions for a 10-bed unit, with 30 participating centers).

3 - Study design

The study is taking care of end-of-life patient with more than 72h hospitalisation families in palliative care unit in a multicentric observational approach.

The families are followed between the 3rd and the 5th day of the admission of the patients in the USP. At 6 months and at 1 year (according to the family's IGC) after the death of the relative in the USP, families are contacted again.

3.1 Inclusion criteria

- The study population consists of the families of patients hospitalized for more than 72 hours for end of life in a palliative care unit.
- All family members present during the admission interview will be included as prolonged grief can be different depending on the experience and background of each.
- The family is defined as being a spouse, partner or companion, parents, children, siblings, cousins.
- An end-of-life stay is defined by the end-of-life qualification by the referring physician who receives the patient.

3.2 Exclusion criteria

- Family not speaking French
- Family refusing to participate in the study
- Family included in another protocol using the same questionnaires
- Hearing-impaired family

- Patient protected by law
- Patient with a life expectancy of <72 hours
- Patient hospitalized for a respite stay

3.3 Population

3.3.1 Population size

Longitudinal family surveillance studies show that 40% are lost to follow-up at 6 months. A total of 500 patients included and 450 evaluable families will detect risk factors for pathological bereavement with an OR value of 2 with an alpha risk value of 0.05 and a Beta risk of 0.2 (assuming the independence of prolonged grief of the members from the same family).

3.3.2 Population analysis

3.3.2.1 Population ITT

All families and patient include in the study.

3.3.2.2 Population PPS

All patients included with a family meeting the inclusion criteria, discharged deceased and stayed more than 3 days in the palliative care unit.

3.4 Visits/Calls

The study will include the following visits and calls:

- The first visit dedicated to patient inclusion.
- The second visit for the start of family follow-up on D3-D5 after admission.
- The psychologist will interview the families of the patients 6 months and 1 year after death, with questionnaires, in a randomized order, assessing the symptoms of anxiety, depression, post-traumatic stress and their experiences during their hospitalization and at the time of death.
- The psychologist will interview families with the characteristics of prolonged grief through phone calls.

4 - Measured variables retained for the analysis

4.1 Demographic

The following demographic data were collected: sex, year of birth, marital status.

4.2 Patient History

The relevant data relating to the patient's history were collected: onset year of the cancerous pathology, diagnosis of the cancerous pathology, metastases, symptoms on admission (dyspnea, pain, infection, deterioration in general condition, nausea / vomiting, obstruction , anxiety / psychological distress, fever, oropharyngeal congestion, convulsions, confusion, coma, respiratory arrest or extreme bradypnea, diarrhoea or other to specific), comorbidities (respiratory, cardiac, renal, hepatic, neurological).

4.3 Gravity score

Several anxiety and depression scores collected are listed below:

- HADS score
 - Symptoms of anxiety (/ 21)
 - Symptoms of depression (/ 21)
- Measurement of post-traumatic stress disorder (I.E.S-R scale) (/ 48)
 - List of difficulties that some people sometimes experience following a stressful event
- IGC score (/ 76)
 - Evaluation of the experience of prolonged or not prolonged grief

5 - Statistical methods

5.1 Descriptive statistics

Each parameter collected will be described for the entire population and according to the main criterion of the study (see section 2.1).

- The qualitative variables will be described by the number and percentage of each variable as well as the number of missing data. Patients with missing data will not be included in the calculation of percentages. The management of the missing data will be carried out according to the studied variable (see section 5.5.2).
- The quantitative variables will be described by the number of observed values, the mean, the standard deviation, the median, the extreme values (minimum and maximum) and the number of missing data. The management of the data (missing, aberrant, incomplete) will be carried out according to the studied variable (see parts 5.5.3 and 5.5.4)

5.2 Statistical tests

All statistical tests will be two-sided at the overall alpha risk level of 5%. A p-value less than 0.1 will be considered statistically significant. All confidence intervals will be two-tailed and presented with a 95% confidence level.

5.3 Duration

The duration (in days) will be calculated by the difference between the start date and end date + 1. (Example, the duration of a drug (days) = drug end date - drug start date + 1).

The duration (in years) will be calculated in the same way.

5.3.1 Treatment of missing data

The missing values for variables in univariate and multivariate analysis will be considered by a simple imputation method if less than 20% missing. Variables with more than 20% missing values will not use in analysis.

5.3.2 Treatment of outliers

In case of outlier's presence, the incidence measurement and prolonged grief in families at 6 months from the date of death risk factors should be evaluated by statistical analysis with the actual values and at least one further analysis, after removing or reducing the outlier's effect.

An outlier's search will be carried out and the measures to be taken will be defined with the Sponsor.

5.3.3 Treatment of incomplete and missing dates

No management of incomplete / missing dates for all events before the study will be carried out. Incomplete / missing dates will be tagged as such in all listings. However, for date-based calculation / sorting / assignment, the actions to be taken will be defined with the Sponsor.

5.3.4 Taking into account biases

In the multivariate model - adjustment on the potential risk factors resulting from the univariate analysis and not collinear with each other. If there is collinearity, we will only keep the variable providing the most information.

5.4 Main analysis

The main goal of the study is to measure the incidence and determine the risk factors for prolonged grief in families 6 months from the date of death.

Analyses were performed on the PPS population without the families with a missing ICG.

Centers with strictly less than 10 patients was grouped together.

The log linearity of all continuous variables was checked. The non-log linear variables were discretized into categorical variables.

If family's main criterion score is strictly greater than 25, it will be considered as a poor outcome.

For the main analysis, we will use univariate mixed logistic regression models to determine which variables will be part of the multivariate model. To consider the correlation of several members within the same family, we will use a center and patient random effect. The variables included in the multivariate model will be the significant ones at the threshold of 0.1 during univariate analysis. A log linearity test will be performed afterwards on the quantitative variables included in the model. If the test is significant, then the variables will be recoded. The variables will then be added in a multivariate mixed logistic regression model while keeping the center and patient random effect. A "backward" selection will be made to select the risk factors retained in the model.

The families with prolonged grief 6 months from the date of death will be the variable to be explained and the explanatory variables will be the potential risk factors.

5.5 Secondary analyzes

The secondary objectives of the study:

- Measurement of the incidence of the HADS score at D3-D5 of admission to the USP.
- Measurement of the incidence and risk factor of the HADS score at 6 months from the date of death.
- Determinants of the evolution of the HADS score between D3-D5 and at 6 months.
- Measurement of the incidence and risk factors of PTSD in families 6 months from the date of death.
- Analysis of the bereavement experience between 6 months and one year after death for families with an ICG > 25

5.5.1 Measurement of the anxiety and depression score of families between D3 and D5 of admission to the USP

An incidence measurement description of the HADS score at D3-D5 of admission to the USP will be made. We will also define the number of families with a score greater than 8.

5.5.2 Measurement of anxiety and depression score of families at 6 months from the date of death and measuring risk factor

Incidence measurement description of the HADS score at 6 months of admission to the USP will be made. We will also define the number of families with a score greater than 8.

Measurement of the anxiety and depression score of families 6 months from the date of death. Same methodology than principal analysis was used for measuring risk factors.

5.5.3 Determinants of the change in the anxiety and depression score of families between D3 and D5 of admission and 6 months from the date of death

Evolution analysis of the HADS score between D3-D5 and 6 months. The scores variation between these two dates will be calculated. Decreasing scores (meaning people situation is getting worse) or stable scores (meaning people condition did not change) will be ranked together against the improving scores.

5.5.4 Measuring the incidence of post-traumatic stress disorder (PTSD) in families 6 months from the date of death and measuring risk factors for PTSD

A description of the measure of the incidence of post-traumatic stress disorder in families at 6 months from the date of death will be made. We will also define the number of families with a score greater than 22. Same methodology than principal analysis was used for measuring risk factors.

5.5.5 Analysis of the bereavement experience between 6 months and one year after death for families with an ICG > 25

Phenomenological interpretative analysis of the interviews carried out with bereaved families with an ICG > 25. The interviews are recorded, transcription of verbatim. The analysis will be done with two psychologists to determine how the bereaved describe the prolonged grief and to highlight the measures of help to be provided.

6 - Computer systems, software and program validation

6.1 System

The analysis will be performed by an ICUREsearch biostatistician. All scans will be performed on Microsoft® Windows 10®.

6.2 Software

The analysis will be performed with SAS® software version 9.4. ICUREsearch reserves the right to use R® software (CRAN) for graphic representations.

6.3 Program validation

The statistician will be responsible for examining each program and the associated SAS® output. The SAS® "Journal" will be saved and examined for logical errors, syntax, and fatal errors.

The raw results of the statistical analysis will be directly generated by the SAS software in the form of a TLF (Tables, Listings and Figures) in pdf format.

The results will be examined for typographical errors, misspellings and absurd values. The consistency of the results will be reviewed with the principal investigator.

7 - Conventions

7.1 Report

All parts of tables, figures and lists are detailed in section 10.4 They will be prepared using SAS[®] software (SAS Institute Inc., Cary, NC, USA) as PDF files (one PDF file per main section).

The footers will be presented as follows: "ICUREsearch SAS - CONFIDENTIAL"

List of page and table configuration requirements:

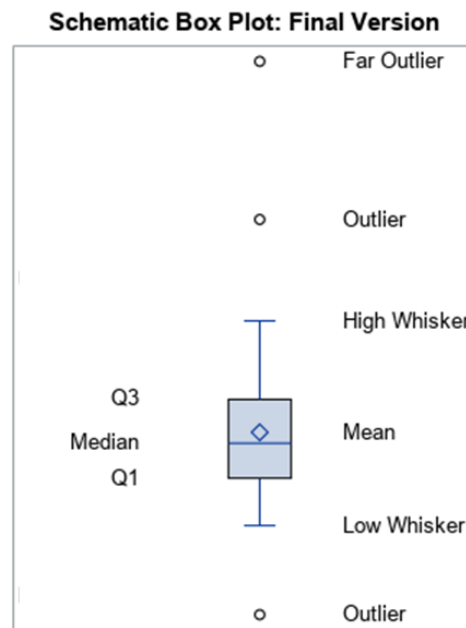
- Font type = Calibri
- Font size = 8 pt (minimum)
- Paper size = A4 (21cm x 29.7cm)
- Page orientation: portrait or landscape as needed
- Graphics: PNG or JPG format

The statistics will be presented as follows:

Parameter	Statistics / Category	Total N=XX
Gender	N	
	NMiss	XX
	Male, n (%)	XX (XX.X)
	Female, n (%)	XX (XX.X)
Height (cm)	N	XX
	NMiss	XX
	Mean (std)	XX (XX.X)
	Median [IQR]	XX [XX ; XX]
	Min / Max	XX / XX

Parameter	Statistics / Category	Cluster 1 (N=XX)	Cluster 2 (N=XX)	P value	Test
Gender	Female, n (%)	XX (XX.XX)	XX (XX.XX)	X.XXXX	Chisq
	Man, n (%)	XX (XX.XX)	XX (XX.XX)		
Height (cm)	Median [IQR]	XX [XX ; XX]	XX [XX ; XX]	X.XXXX	M-W

The boxplots will be presented as follows:



An individual is considered an outlier when the value of it is less than 1.5 times the interquartile range from Q1, and more than 1.5 times the interquartile range from Q3. It is considered far outlier when this value is less than 3 times the interquartile range from Q1 and more than 3 times the interquartile range from Q3.

Example: We want to represent the boxplot of the size of the individuals in our population. We have the first quartile (Q1) at 160 cm, the median at 170 cm and the third quartile (Q3) at 180 cm. The interquartile range is $Q3 - Q1 = 180 - 160 = 20$.

$1.5 * 20 = 30$, $Q3 + 30 = 180 + 30 = 210$ cm, $Q1 - 30 = 160 - 30 = 130$ cm.

So, if an individual is less than 130cm or more than 210cm, he will be considered an outlier.

$3 * 20 = 60$, $Q3 + 60 = 180 + 60 = 240$ cm, $Q1 - 60 = 160 - 60 = 100$ cm.

So, an individual will be considered far outlier if he is less than 100 cm and more than 240 cm.

8 - Appendices

8.1 Appendix 1 – Study flow chart

	Visit 1 : initial	Visit 2 : D3-D5 after admission	Call 3 : 6 months after death	Call 4 : Between 6 months and 1 year after death
	Inclusion	Follow		End
	Coordinating center	Coordinating center	Coordinating center	Coordinating center
Subject information / Consent	X			
Inclusion / exclusion criteria	X			
Patients variables	X			
Family variables	X			
Family follow-up :				
HADS		X	X	
HADS			X	
PTSD			X	
IGC			X	
FAMI-LIFE			X	
Qualitative analysis for families with a CGI <25				X

8.2 Appendix 2 – Derived data

VARIABLE	DEFINITION / CALCUL
Duration in USP	USP Release Date - USP +1 entry date. Length of time the patient was in USP.
Pathology duration	Year of entry into USP - Year of onset of the pathology +1. Duration between the start of the pathology and the date of admission to the USP.
Patient's age	Year of entry into USP - Year of birth of the patient. Patient's age when entering the USP
Family age	Year of creation of the family - Year of birth of the family. Age of the family member when the patient entered the USP.
Total HADS D3D5 score for anxiety	Sum of HADS score between days 3 and 5 after admission for anxiety (A).
Total HADS score D3D5 for depression	Sum of HADS score between days 3 and 5 after admission for depression (D).
Total HADS score D3D5	Total HADS score for A + Total HADS score for D between days 3 and 5 after admission.
HADS score D3D5	Binary variable coded 1 if the HADS score is greater than or equal to 8 and 0 otherwise. Calculated only for family members with a HADS total score between days 3 and 5 after admission.
Total HADS score at 6 months for anxiety	Sum of HADS score at 6 months after death for anxiety (A).
Total HADS score at 6 months for depression	Sum of HADS score at 6 months after death for depression (D).
Total HADS score at 6 months	Total HADS score for A + Total HADS score for D at 6 months of death.
HADS score at 6 months	Binary variable coded 1 if the HADS score is greater than or equal to 8 and 0 otherwise. Calculated only for family members with a HADS total score at 6 months after death.
Total PTSD score at 6 months	Total PTSD score at 6 months
PTSD score	Binary variable coded 1 if the PTSD score is greater than 22 and 0 otherwise. Calculated only for family members with a PTSD total score at 6 months after death.
Total IGC score at 6 months	Sum of IGC score at 6 months after death.
IGC score at 6 months	Variable binaire codée 1 si le score IGC est supérieur à 25 et 0 sinon. Calculé uniquement pour les membres de la famille ayant un score total IGC à 6 mois.

VARIABLE	DEFINITION / CALCUL
Date of death	Date of discharge from the USP when the patient died. Applies only to patients who have died in USP.

8.3 Appendix 3 – SAS® procedure

Description of a quantitative variable:

```
PROC MEANS Data = TABLE n nmiss mean min max std median q1 q3 maxdec=2;  
    Var QUANTI;
```

RUN;

With QUANTI for the quantitative variables TABLE the data on which the analyzes are carried out.

Description of a qualitative variable:

```
PROC FREQ Data = TABLE ;  
    Table QUALI ;
```

RUN ;

With QUALI for the qualitative variables TABLE the data on which the analyzes are carried out.

Application of logistic regression on a quantitative variable and a binary qualitative variable:

```
PROC GLIMMIX Data = TABLE ;  
Class ALEA ;  
Model VARY (event = « 1 ») = VARX /dist = binary link = logit ddfm = satterth solution cl ;  
Random intercept / subject=ALEA ;  
RUN ;
```

With TABLE the data on which the analyzes are carried out, ALEA the random effect, VARY the variable to be explained representing the main criterion, VARX the binary quantitative or qualitative explanatory variable.

Application of logistic regression on a qualitative variable in classes :

```
PROC GLIMMIX Data = TABLE ;  
Class VARX ALEA ;  
Model VARY (event = « 1 ») = VARX /dist = binary link = logit ddfm = satterth solution cl ;  
Random intercept / subject=ALEA ;  
RUN ;
```

With TABLE the data on which the analyzes are carried out, ALEA the random effect, VARY the variable to be explained representing the main criterion, VARX the qualitative explanatory variable in classes.