C-EASIE Study

Statistical Analysis Plan

Final Version 1.0

Project Title: C-EASIE trial: Vitamin C - Early Administration in Sepsis In ED

Date: 23 November 2023

Version: Final Version 1.0

1 Contents

2 Purpose

This document provides details for the statistical evaluation of the primary and secondary endpoints of the C-Easie trial

3 Description of the Study

A total of 300 patients were to be randomised in a 1:1 ratio to either Placebo or Intervention. Randomisation was stratified by study site.

4 Study Objectives and Endpoints

4.1 Study Objective

The objective of the C-Easie trial is to evaluate the clinical efficacy of early administration of Vitamin C in addition to the standard of care in patients hospitalized with sepsis or septic shock.

4.2 Study Endpoints

4.2.1 Primary Outcome

Average post-baseline patient SOFA score (on day 2-5 after patient inclusion).

4.2.2 Secondary Outcomes

The following secondary outcomes will be of interest:

- Day-specific SOFA score (day 2-5)
- Maximum SOFA score (day 2-5)
- 28-day mortality
- Length of hospital stay
- Length of ICU stay
- Vasopressor requirement: total duration and dosage
- RRT duration and need
- Ventilator days
- Total dose of steroids given
- Lab values :
    - Creatinine, CRP on d2-d5
    - Procalcitonin on d4
- Quality of life (EQ-5D-5L)
- Time to return to work (if applicable)

5 Sequence of Planned Analyses

5.1 Interim Analyses

No formal interim analyses to check for early efficacy or futility have been planned.

A blinded interim analysis for sample size recalculation was planned after 12 months (or at the latest if 75% of the planned number of subjects is recruited) to monitor the assumed variability of the SOFA score (cfr infra), the assumed correlation between the time points and the assumed dropout rate. If the observed standard deviation, dropout rate and correlations deviate from the assumed values such that the desired power level of 80% is not guaranteed anymore, an increase of

the planned sample size will be considered. If the power level is at least 80% with the observed values, the sample size will remain unaltered.

A review of the safety data is performed by a Data Safety Monitoring Board (DSMB).

5.2 Early Termination

Early termination of the study is possible if recommended by the DSMB to stop due to safety concerns.

5.3 Final Analysis and Reporting

Upon final database lock, statistical analyses of the data will be performed according to the methods described in this document.

The analysis populations and analysis plan will be finalised at a Blinded Review Meeting prior to database lock. The Blind Review Meeting will be attended by the Principal Investigator, Study Statistician and other relevant study personnel. Attendees will be kept blind from randomised study treatment. All decisions taken at this meeting will be fully documented in a Blind Review Document that will be dated and signed prior to final database lock.

The agenda of the Blind Review Meeting will include (but not necessarily be limited to) the following:

- Definition of Per Protocol Set
- Definition of Subgroup analysis
- Pooling of Study Sites

6 Sample Size Determination

The required sample size is calculated to detect with at least 80% power a difference in average post-baseline patient SOFA score (calculated over days 2 to 5), based on a constrained longitudinal data analysis model with alpha set at 0.05 (Liang and Zeger, 2000). The power is calculated using an approach presented by Stroup (Stroup, 1999) . In the cLDA, both the baseline and post-baseline value are modeled as dependent variables, as opposed to a (longitudinal) ANCOVA model in which the baseline value is included as a covariate. Although the baseline measure is included in the response vector in cLDA, the true baseline means are constrained to be the same for different treatment groups due to randomization, and this analysis provides an adjustment for the observed baseline difference in estimating the treatment effects. Since the randomization is performed within center, considering center as an effect in the analysis has no impact on the sample size. Patients who die within the time period of 5 days receive the worst outcome (highest SOFA score) starting at the day of death. Based on the cLDA model, 126 patients per group (252 patients in total) are needed to detect with at least 80% power a difference between the control and intervention group of 1 in average post- baseline SOFA score. A standard deviation of the SOFA score equal to 3.5 and a correlation between the time points equal to 0.5 was assumed. These were conservative estimates, derived from reported information in two studies (Fowler et al, 2019; Fujii et al. 2020). 2.5%, 5%, 10% and 15% missing values are assumed on d2, d3, d4 and d5, respectively (combination of dropout and mortality). However, the sample size will be increased to 150 patients per group to anticipate a larger variability due to the imputation of one or more maximal SOFA scores for deceased patients.

7 Analysis Populations

The following analysis sets will be of interest:

7.1 Full Analysis Set (FAS)

The FAS will include all randomised patients according to their randomised treatment. However, some randomised patients will be excluded from the FAS, as decided during the Blind Review Meeting(s). A list of these patients can be found in the report of this meeting.

The FAS will be used for the evaluation of all efficacy and safety endpoints.

7.2 Safety Set (SS)

No separate Safety Set will be defined.

The FAS will be used for the evaluation of all safety parameters.

7.3 Per Protocol Set (PPS)

The Per Protocol Set will be reviewed and finalized prior to database lock at the Blind Review Meeting.

As decided during the Blind Review Meetings (September 25, 2023 and October 23, 2023) patients from the FAS with the following protocol deviations will be excluded from the per protocol set (PPS):

- Patients with 7 hours or more between hospital admission and first administration of study medication.
- Two or more successive doses missed due to other reasons than early discharge or death. If exact timing of missed doses is not available, patients with two doses missing on the same day.
- All planned doses missing on the first day (note that depending on the hour of randomisation, the number of planned doses might can be one).

The PPS will be used for the evaluation of all efficacy endpoints.

8 General Issues for Statistical Analysis

8.1 Analysis Software

All analyses will be performed using SAS software, version 9.4 of the SAS System for Windows. Copyright © 2002 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA

8.2 Summary Statistics

Continuous variables will be summarized by treatment group by the number of non-missing data points, mean, standard deviation, median and interquartile range.

Categorical and ordinal variables will be summarized by treatment group by observed frequencies and percentages relative to the total number of non-missing items.

All summary statistics will be presented by treatment group and, where relevant, overall.

Day 1 is defined as the day of randomization.

8.3 Centre Effect

All statistical analyses of the outcomes of interest will be adjusted for study site. When applying the adjusment, the small site ULB Erasme (3 patients in the FAS) will be combined with UZ Brussels (Jette), as decided during the Blind review meeting (September 25, 2023).

9 Methods for Missing Data

In the statistical analyses of the longitudinally measured outcomes the presence of missing values is handled using a direct likelihood approach to fit the multivariate models. As such, the analysis is valid under the missing at random assumption (MAR).

Handling missing data for the SOFA score

In some settings, the following rules for single imputation will be used to handle missing SOFA scores or missing components for the calculation of the SOFA score.

- Patients who die within the time period of 5 days receive the worst outcome (highest SOFA score being equal to 24) starting at the day of death (even if a SOFA score is available at the day of death).
- SOFA scores are considered missing after the day of discharge
- If the patient's status does not require a lab analysis (due to good condition of the patient), missing data occur as per protocol. In this case the best possible score will be used for the SOFA score calculation (i.e. 0 points for bilirubin, blood platelets and creatinin) in the daily follow-up.
- If however a lab analysis was not ordered but was required as per protocol, the SOFA score of that day will be considered as missing.
- If a lab analysis was required, but one of the three lab values needed in the SOFA score was missing, the previous lab value was used for the calculation of the SOFA score. This was deemed appropriate, since it can be assumed that the specific lab parameter was not ordered that day because the function was considered stable. In rare cases where this happened at d1, the value of d2 will be used for the calculation of the SOFA score.

Frequency tables will be reported for the various settings where above imputation rules were applied.

For the analysis of the maximal SOFA score a multiple imputation approach will be used (cfr infra for details of the imputation model).

10 Data Transformations

An inverse hyperbolic sign transformation will be applied in the analysis of the (maximal) SOFA to obtain a more symmetric distribution of the model residuals. Analyses on untransformed scores will be reported as sensitivity analyses.

11 Multicenter Study

All analyses will be adjusted for study site if feasible. No adjustment will be considered for binary outcomes (or time-to-event outcomes) when a low number of events yields computational problems.

12 Stratification Factors

Randomization was stratified for study site. Therefore, all models that are used for the estimation of treatment effects will be adjusted for study site.

13 Multiple Comparisons

Since only 1 primary endpoint is defined, no adjustment of the significance level is required.

For secondary efficacy endpoints, due to the exploratory nature of the efficacy analyses, no adjustment for multiple comparisons will be made.

14 Planned Subgroups, Interactions and Covariates

Moderator analyses will be performed for the primary outcome.

It will be verified if the treatment effect depends on the following baseline variables:

- baseline SOFA
- baseline NEWS score

For the baseline SOFA score, subgroups will be defined (<6 vs >=6). Appropriate summary statistics per treatment arm and estimated treatment effects will be presented for each subgroup. In addition, the interaction between the above subgroups and treatment effect will be tested to assess whether the treatment effect differs according to subgroup.

The baseline NEWS score will be evaluated as a continuous moderator by including the main effect of the baseline NEWS score and the interaction between the baseline NEWS score and the treatment effect in the analysis model, allowing non-linearity for the relation of the baseline NEWS score (using restricted cubic splines with 4 knots).

Subgroup analyses will only be performed for the FAS.

15 Disposition of Study Subjects

A summary by treatment group will be provided for the following:

- Number of randomized subjects,
- Number treated according to randomization
- Number in Full Analysis Set (FAS)
- Number in Per Protocol Set (PPS)
- Exclusions from FAS
- Exclusions from PPS
- Number of subjects who died in hospital up to Day 5
- Number of subjects who were discharged up to Day 5

16 Demographics and Other Baseline Characteristics

All data recorded at baseline will be summarized by treatment group. Since it is a randomised study, no statistical tests will be performed to compare these data between the groups.

Summaries will be presented for FAS and PPS separately.

The following baseline information will be presented:

- Age, (y)
- Sex
- Weight (kg)
- NEWS score at ED presentation
- SOFA score at d1, and the constituing components, i.e.
  - GCS score
  - Use of vasopressors and MAP
  - Bilirubin (mg/dL)
  - Creatinin (mL/day)
  - Platelets
  - PaO2/FiO2 ratio
- Sepsis or septic shock (defined as (MAP <70 or use of vasoactive agents) and (lactate>2 mml/L))
- Sepsis etiology, No (%)
  - Respiratory
  - Gastro-intestinal
  - Urinary
  - Skin or soft tissue
  - Catheter
  - Other/unknown
- Physiological variables (d1)
  - Serum creatinine, mg/d
  - Procalcitonin, ng/ml
  - CRP, mg/l
  - Sodium, mmol/l
  - Lactate, mmol/l
- Interventions during admission, Y/N + # days
  - Mechanical ventilation
  - Vasopressors
  - Renal replacement therapy
- IV fluids
  - Total of IV fluids administered at d1
- Time from ED presentation to 1st dose of Vitamin C
  Time to 1st antibiotic

Mean (SD) and median (IQR) will be reported for all continuous variables.

17 Primary and Secondary Endpoints

All used tests are two-sided and alpha is set at 0.05 for the primary as well as for the secondary outcomes.

17.1 Primary Efficacy Endpoint: mean SOFA score d2-d5

Summary and statistical analysis of the primary endpoint will be done using the FAS and the PPS.

The primary analysis compares the average post-baseline patient SOFA score (average over days 2-5). The average post-baseline score will be compared between both groups with a two-sided test derived from a constrained longitudinal data analysis (cLDA) model using a likelihood approach with alpha equal to 0.05 and a Kenward-Roger approximation of the denominator degrees of

freedom. Rules to handle missing SOFA scores are discussed in section 10. The choice of the covariance structure for the five measurements in the cLDA model will be based on the Aikake criterion. Site will be added as a fixed factor in the model. The cLDA analysis is valid under the missing at random assumption (MAR) and assumes that the probability that an observation is missing depends only on observed values of the individual, but not on the missing ones. An inverse hyperbolic sign transformation will be applied to handle the (right-)skewed distribution of the SOFA scores. Results will be presented after back-transformation to the original scale. As such, the estimate for the treatment effect will refer to a ratio instead of to a difference. Results on untransformed SOFA scores will be reported as sensitivity analyses.

17.2 Secondary Efficacy Endpoints

Summaries and statistical analyses of the secondary endpoints will be done using the Full Analysis Set and the Per Protocol Set.

17.2.1 Length of hospital stay

To evaluate differences in length of hospital stay, death during hospital (ICU) stay will be treated as a competing risk (Brock et al. 2011), using a stratified Gray's test for the comparison of both groups. Patients not yet discharged will be censored.

17.2.2 Length of ICU stay

The same approach as for length of hospital stay will be used. The analysis will be restricted to patients admitted in ICU. Note however that the time starts at the moment of ICU admission and not at the moment of randomisation (this to handle the possibility that patients need to go the ICU at a later moment during the follow-up).

17.2.3 SOFA score at d2-d5

From the cLDA model used for the primary endpoint, mean values at d2, d3, d4 and d4 will be compared with two-sided tests and 95% confidence intervals will be reported.

17.2.4 Maximal SOFA score during d2-d5

The maximal SOFA score will be compared using a two-sided unpaired t-test after inverse hyperbolic sign transformation. For patients who are discharged, the observed maximum SOFA will be used. If there are patients with a missing SOFA score due to administrative reasons, a multiple imputation approach (20 imputed datasets) will be considered since the observed maximum can be underestimated for these patients. Multivariate imputation will be performed for the daily SOFA scores using the fully conditional specification (FCS) approach (Van Buuren et al., 2007), separately in each treatment arm. For the imputation, linear models will be specified for each daily SOFA score (ordered d5-d1) with as regressors the SOFA scores on the other days. The seed value will be set at 15112023.

17.2.5 28-day mortality

28-day mortality will be compared using a stratified χ^2 test (study site as stratum). 95% confidence intervals will be reported for the percentage mortality in each treatment group and for the odds ratio. However, when there are subjects lost to follow-up before 28 days, 28-day estimates will be

derived from the Kaplan-Meier curve and compared using a Z-test (on the complementary log-log scale).

17.2.6 Vasopressor requirement

The vasopressor requirement will be compared using a generalised linear mixed model (i.e. a logistic regression model with a random effect of patient). An odds ratio will be reported comparing the use over d2-d5, as well as the timepoint specific use. Study site will be added in the model. Note that the model will be fit on information from d1-d5. Note that the mean duration of vasopressor requirement (i.e. in the period d2-d5) can be derived directly from this model as the sum of the daily probabilities. Vasopressor requirement is an ordinal scale (4 levels starting with 'no') and results will be reported from separate models using the three possible cutpoints (for example 'no' versus 'yes').

For discharged patients, no vasopressor requirement is assumed. For deceased patients, requirement and dosage are put on missing from that day on (in case information was available on the day of death, the information is considered missing from the day after death on).

17.2.7 Renal replacement therapy

The probability of renal replacement therapy (RRT) will be compared using a generalised linear mixed model (i.e. a logistic regression model with a random effect of patient). An odds ratio will be reported comparing the 'mean probability' over d2-d5. Given the expected low number of events, for the timepoint specific RRT only descriptives will be reported. RRT is put on zero when the patient is discharged. When a subject is deceased, the value is considered missing from that day on (in case RRT information was available on the day of death, the information is considered mising from the day after death on). Note that the model will be fit on daily information from d1-d5 and that the mean duration of RRT (i.e. in the period d2-d5) can be derived directly from this model as the sum of the daily probabilities.

17.2.8 Mechanical ventilation

The probability of mechanical ventilation (MV) will be compared using a generalised linear mixed model (i.e. a logistic regression model with a random effect of patient). An odds ratio will be reported for the comparison of the 'mean probability' over d2-d5, and for the day-specific odcomparisons. MV is put on zero when patient is discharged. When a subject is deceased, the value is considered missing from that day on (in case MV information was available on the day of death, the information is considered missing from the day after death on). Note that the model will be fit on daily information from d1-d5 and the mean duration of MV (i.e. in the period d2-d5) can be derived directly from this model as the sum of the daily probabilities.

17.2.9 Dose and need of steroids

The daily dose of steroids given will be compared between both groups using a multivariate normal model for longitudinal measurements, with the Aikake criterion to select the covariance matrix. The mean dosage over d2-d5 will be compared, as well as the timepoint specific dosages. Study site will be added in the model. Note that the model will be fit on information from al patients in the period d1-d5. For discharged, lost-to-FU and deceased patients, the dose will be put on missing.

The need of steroids (MV) will be compared using a generalised linear mixed model (i.e. a logistic regression model with a random effect of patient) with site added as a fixed effect. An odds ratio will be reported for the comparison of the 'mean probability' over d2-d5, and for the day-specific comparisons.

17.2.10 IV fluids

Within the group of patients admitted in the ICU the daily fluid balance (ml) will be compared between both groups using a multivariate normal model for longitudinal measurements, with the Aikake criterion to select the covariance matrix. The mean over d2-d5 will be compared, as well as the timepoint specific value. Study site will be added in the model. Note that the model will be fit on information from d1-d5, but restricted to the days the patient is in the ICU. For patients who die during ICU, the balance will be put on missing.

17.2.11 Quality of life (EQ-5D-5L)

The total scores will be compared between both groups using a multivariate normal model for longitudinal measurements, with the Aikake criterion to select the covariance matrix. the timepoint specific dosages. Study site will be added in the model. Note that the model will be fit on information from baseline – day 5 (or day of discharge if discharge before day 5), day 28 and month 3. For lost-to-FU and deceased patients, the score will be put on missing. Comparisons will refer to the three specific timepoints after baseline.

17.2.12 Return to work

For patients who were at work before inclusion in the study, the time until return to work will be compared. Patients lost-to-FU and patients not returned to work (at three months) are censored. Deceased patients are treated as a competing risk. The comparison will be based on a stratified Gray's test.

18 Adverse Events

The number of events and the number of patients experiencing adverse events will be summarized by treatment group.

Separate summaries will be presented for:

- Serious adverse events
- Serious or severe adverse events
- Treatment-related adverse events
- Treatment-related serious adverse events.

Summaries of adverse events will be presented only for the FAS.

19 Other Data

All other data will be summarized by treatment group and, if applicable, by day.

20 References

- Brock GN, Barnes C, Ramirez JA, Myers J. How to handle mortality when investigating length of hospital stay and time to clinical stability. BMC Med Res Methodol. 2011;11. doi:10.1186/1471-2288-11-144
- Fowler AA, Truwit JD, Hite RD, et al. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients with Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. In: JAMA - Journal of the American Medical Association. Vol 322. American Medical Association; 2019:1261-1270. doi:10.1001/jama.2019.11825
- Fujii T, Luethi N, Young PJ, et al. Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support among Patients with Septic Shock: The VITAMINS Randomized Clinical Trial. In: JAMA - Journal of the American Medical Association. Vol 323. American Medical Association; 2020:423-431. doi:10.1001/jama.2019.22176
- Liang K-Y, Zeger SL. Indian Statistical Institute Longitudinal Data Analysis of Continuous and Discrete Responses for Pre-Post Designs. Indian J Stat Ser B Ser B Biostat. 2000;62(1):134-148. doi:10.2307/25053123
- SAS software, version 9.4 of the SAS System for Windows. Copyright © 2002 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA
- Stroup, W. Mixed model procedures to assess power, precision, and sample size in the design of experiments. Proc. Biopharmaceutical Section. Am. Stat. Assoc., Baltimore, MD 15-24 (1999).
- Van Buuren, S. (2007), “Multiple Imputation of Discrete and Continuous Data by Fully Conditional Specification,” Statistical Methods in Medical Research, 16, 219–242.

Addendum 1: Calculation of SOFA score

GCSc=categorised Glasgow Coma Score (GCS).
    15: 15
    16: 13-14
    17: 10-12
    18: 6-9
    19: <6
Platelets= categorised platelets (×103/µL)
    1: ≤150
    2: 100-149
    3: 50-99
    4: 20-49
    5: <20
BilirubinC=categorised bilirubin in mg/dL (or µmol/L)
    1: <1.2 (<20)
    2: 1.2-1.9 (20-32)
    3: 2.0-5.9 (33-101)
    4: 6.0-11.9 (102-204)
    5: ≥12.0 (>204)

CreatinineC=categorised creatinin in mg/dL (or µmol/L)
    1: <1.2 (<110)
    2: 1.2-1.9 (110-170)
    3: 2.0-3.4 (171-299)
    4: 3.5-4.9 (300-400) or UOP<500mL/day
    5: ≥5 (>440) or UOP<200mL/day
VasoDose=categorised administered vasoactive agents (mcg/kg/min)
    1: dopamine ≤ 5 or dobutamine (any dose)
    2: dopamine > 5 epinephrine ≤ 0.1 or norepinephrine ≤0.1
    3: dopamine > 15 epinephrine > 0.1 or norepinephrine> 0.1
MAPc=categorised mean arterial pressure (mmHg)
       1: ≥70
       2: <70
PaO2FiO2c=categorised PaO2/FiO2(mmHg)
       1: ≥400
       2: 300-399
       3: 200-299
       4: ≤199 and NOT mechanically ventilated
       5: 100-199 and mechanically ventilated
       6: <100 and mechanically ventilated
O2FiO2c O2Sat/FiO2(mmHg)
       1: > 400
       2: ≤ 400
       3: ≤ 315
       4: ≤ 235
       5: ≤ 150
lab_anal_day: was a lab analysis ordered?
       0: No
       1: Yes
nolab_analreas_day: Why was a lab analysis not ordered?
       1: not needed due to the good condition of the patient
       2: lab analysis was forgotten
Fudate: follow-up date
Deathdate: day of death

```
SOFA=0;
 if GCSc=15 then SOFA=SOFA+0;
 if GCSc=16 then SOFA=SOFA+1;
 if GCSc=17 then SOFA=SOFA+2;
 if GCSc=18 then SOFA=SOFA+3;
 if GCSc=19 then SOFA=SOFA+4;
 if PlateletsC=1 then SOFA=SOFA+0;
 if PlateletsC=2 then SOFA=SOFA+1;
 if PlateletsC=3 then SOFA=SOFA+2;
 if PlateletsC=4 then SOFA=SOFA+3;
 if PlateletsC=5 then SOFA=SOFA+4;
 if BilirubinC=1 then SOFA=SOFA+0;
 if BilirubinC=2 then SOFA=SOFA+1;
 if BilirubinC=3 then SOFA=SOFA+2;
 if BilirubinC=4 then SOFA=SOFA+3;
 if BilirubinC=5 then SOFA=SOFA+4;
 if CreatinineC=1 then SOFA=SOFA+0;
 if CreatinineC=2 then SOFA=SOFA+1;
 if CreatinineC=3 then SOFA=SOFA+2;
 if CreatinineC=4 then SOFA=SOFA+3;
 if CreatinineC=5 then SOFA=SOFA+4;
 if VasoDose=. then do;
       if MAPc=1 then SOFA=SOFA+0;
       if MAPc=2 then SOFA=SOFA+1;
                      end;
 if VasoDose^=. then do;
       if VasoDose=1 then SOFA=SOFA+2;
       if VasoDose=2 then SOFA=SOFA+3;
       if VasoDose=3 then SOFA=SOFA+4;
                       end;

 if PaO2FiO2c=1 then SOFA=SOFA+0;
 if PaO2FiO2c=2 then SOFA=SOFA+1;
 if PaO2FiO2c=3 then SOFA=SOFA+2;
 if PaO2FiO2c=4 then SOFA=SOFA+2;
 if PaO2FiO2c=5 then SOFA=SOFA+3;
 if PaO2FiO2c=6 then SOFA=SOFA+4;

 if O2FiO2c=1 then SOFA=SOFA+0;
 if O2FiO2c=2 then SOFA=SOFA+1;
 if O2FiO2c=3 then SOFA=SOFA+2;
 if O2FiO2c=4 then SOFA=SOFA+3;
 if O2FiO2c=5 then SOFA=SOFA+4;


*deceased patients receive maximal score from the day of death on;
 if Fudate>=Deathdate>.z then SOFA=24;

*when lab analysis is forgotten, SOFA is put on missing;
 if nolab_analreas_day=2 then SOFA=.;

*when info is missing if a lab analysis was performed, SOFA is put on missing;
 if lab_anal_day<=.z then SOFA=.;

*if no lab analysis is performed and there is no information on the reason of a
missing lab analysis, SOFA is put on missing;
 if lab_anal_day=0 and nolab_analreas_day not in (1,2) then SOFA=.;
```