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Title: Statistical modelling to analyse health-related quality of life outcomes in randomised clinical trials in oncology

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Statistical modelling to analyse health-related quality of life outcomes in randomised clinical trials in oncology

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Abstract

Randomised controlled clinical trials are commonly designed to study the efficacy of a new drug. Health-related quality of life (HRQoL) outcomes have been increasingly recognized as an important endpoint in cancer treatment. Recent reviews show little consensus on the analysis, interpretation, and reporting of these data from a statistical perspective.

In this project, we aim to understand the strengths and limitations of the current statistical approaches to evaluate quality of life data. Linear model, generalised and linear mixed models, the beta-binomial distribution, time-to-event analysis and missing data analysis will be explored.

Additionally, the above approaches will be used to analyse the patient-reported HRQoL of the breast cancer phase II of the Coralleen trial (NCT03248427).

Keywords: Longitudinal data analysis, mixed model, quality of life, clinical trials, survival analysis, ordinal outcomes

MSC2000: 62-07 Data analysis, 62P10 Applications to biology and medical sciences

Summary

1. Introduction

1.1 State of the art

Randomised controlled clinical trials are commonly designed to study the efficacy of a new drug and its impact on patients' quality of life[1]. The health-related quality of life (HRQoL) outcomes has been increasingly recognized as an important endpoint in cancer treatment and several validates questionnaires are available to collect this information[2]. Nevertheless, in terms of drug approval the main interest falls in the result of the efficacy outcomes and quality of life results are commonly reported as a secondary finding.

In the specific field of breast cancer, a success in drug development has been observed in the last decade with several treatments that have significantly improved the prognosis of patients[3 4 5]. However, at the same time, a decline in the overall quality of life has been reported in some subgroup of patients[6]. Recent systematic reviews of the most used statistical methods to study HRQoL in breast cancer showed a little consensus about the analysis, interpretation, and reporting of these data from a statistical perspective[7 8]. As a consequence, some of the publications that report quality of life outcomes tends to use a simple but non-optimal statistical approach for data analysis that could bias the findings and let to incorrect conclusions[7].

In parallel, a randomised phase II clinical trial was conducted to evaluate the treatment of neoadjuvant poli-chemotherapy in comparison with letrozole plus ribociclib (L+R) in postmenopausal women with hormone receptor-positive, HER2-negative, Luminal B breast cancer (Coralleen trial, NCT03248427). Letrozole (L) is an endocrine therapy and ribociclib (R) is a cyclin-dependent kinases 4 and 6 (CDK4/6) inhibition. The trial was designed with the hypothesis that endocrine therapy in combination with CDK4/6 inhibition (in this case L+R) could represent an alternative to multiagent chemotherapy. The primary efficacy analysis was already published and showed similar results in both treatment groups, with a similar proportion of patients with low-risk risk of recurrence at surgery (46.9% vs. 46.1%)[9]. However, the improvement in patient's quality of life with a chemotherapy-free strategy is still unknown.

1.2 TFM proposal

The analysis of longitudinal data has always been an issue of personal interest. The majority of real-world outcomes changes over time and the study of those outcomes in a longitudinal perspective could provide a better understanding that using a cross-sectional approach. From a biostatistical perspective, the study of quality of life data presents a challenge due to the nature of this type of data. However, my current knowledge on statistical modelling to analyse HRQoL outcomes is poor. The TFM project is the opportunity to deeply study the HRQoL outcomes and to better understand the strengths and limitation of the statistical methods to analyse quality of life outcomes. Additionally, the SOLTI Group (an academical research group in breast cancer) conducted a randomised trial and collected quality of life data still unexplored. Altogether, this project could improve my

theoretical statistical knowledge and it could help in the analysis of the quality of life data of the phase II Coralleen trial.

In this TFM project, we aim 1) to understand the available questionnaires to collect patient's HRQoL outcomes, 2) to understand the strengths and limitations of the current statistical approaches to evaluate quality of life data, 3) to provide practical recommendations in the analysis of HRQoL data, 4) to analyse the patient-reported HRQoL of the phase II Coralleen study and 5) to elaborate a manuscript to publish the findings in the quality of life analysis of the phase II Coralleen study.

1.3 Structure of the work

This project will be divided into seven chapters. In the first chapter we have described the current situation of the HRQoL analysis in the oncology field and we have presented the objectives of this work.

In the second chapter, we will introduce and define the term HRQoL and the most used validate questionnaires to collect those outcomes. Additionally, we will explore in detail the structure and the score punctuation of one of the most famous questionaries (EORTC QLQ-C30). The third chapter is dedicated to formally define the statistical modelling for the analysis of quality of life data. Linear regression, mixed models, beta-binomial approach, multiple pairwise comparison, time-to-event analysis and missing data analysis will be explored and discussed.

In the fourth chapter, we will contextualize the Coralleen trial. The trial design, the objectives and the published efficacy data analysis will be detailed. Next, we will study the quality of life data from the Coralleen trial. First, we will perform a descriptive analysis of the trial data and the latter we will apply the regression modelling strategies already defined in the third chapter. The statistical results will be reported along with the most relevant graphical approaches to interpret and communicate the quality of data results.

In the sixth chapter we will discuss practical recommendations for the statistical analysis of HRQoL data. To finish the project, the conclusions of the work will be summarized as well as the most relevant points to be explored in future research.

2. Health-related quality of life (HRQoL)

The inclusion of health-related quality of life (HRQoL) measures in medical research has become common in oncology clinical trials and has been increasingly recognized as an important endpoint in cancer treatment. The HRQoL is typically evaluated by patient-reported outcomes (PROs) and can be assessed by using validated instruments[10]. PROs are defined as direct feedback on a patient's health condition from a patient's perspective and, therefore, PRO scores reflect the individual HRQoL without external interpretation[11]. Consequently, patients are the primary source of information regarding his/her subjective HRQoL.

In the current work, we will focus on HRQoL used in the context of breast cancer clinical trials. In the past few years, a rapid improvement has been observed in treatment strategies for breast cancer with chemotherapy, endocrine therapy and targeted immunotherapy agents. In terms of efficacy, this has been associated with an improvement of the prognosis of patients with breast cancer in the early and metastatic setting[3 4 5 6]. However, in a recently published report by Cardoso and colleagues[6], a decline in the overall quality of life in metastatic breast cancer patients was observed over the last decade. Those findings suggest that the success in breast cancer drug development in the last decade is associated with an improvement of treatment efficacy, but not necessarily with a better patient's HRQoL outcomes.

Considering this background, the evaluation and the correct statistical analysis of the PROs is crucial to understand the clinical benefit and the impact in patient satisfaction of the different treatment strategies.

2.1 Measurements of HRQoL

Since the creation of the concept of HRQoL, several research organizations have developed questionnaires to transform this subjective evaluation into measurable scores. It is generally accepted that HRQL is a multidimensional construct incorporating at least three broad domains: 1) physical, 2) psychological and 3) social functioning that are affected by one's disease and/or treatment[12].

- Physical functioning is usually defined as the ability to perform a range of activities of daily living, as well as physical symptoms resulting either from the disease itself or from treatment.
- Psychological functioning ranges from severe psychological distress to a positive sense of well-being and may also encompass cognitive functioning.
- Social functioning refers to quantitative and qualitative aspects of social relationships and interactions, and societal integration.
- In addition, there is consensus that HRQL assessments also entail an overall judgement of health quality of life.

Patients are usually asked to inform regarding his/her HRQoL in different study time points. The longitudinal collection of PROs provides a short-term information about the patient's status, but also a signal change over time. As mentioned previously, in the current work we will focus in PROs used in the context of breast cancer clinical

trials. A couple of reviews performed in 2021 identified that the most used PROs validated questionnaires in the context of clinical trials are the following[8 10]:

- European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30)[13]
- EORTC QLQ-BR23 (breast cancer specific)[14]
- 36-Item Short Form Survey (SF-36)[15]
- Functional Assessment of Cancer Therapy–Breast Subscale (FACT-B)[16]
- EuroQoL (EQ)-5D[17]

2.2 Example of HRQoL questionnaire

The most used HRQoL in oncology is the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30)[8]. In this section we will detail the structure and the score punctuation of this validated questionary to understand with a practical example the type of quality of life data that can be obtained in clinical trials.

The EORTC quality of life questionnaire is an integrated system for assessing HRQoL of cancer patients participating in international clinical trials. The EORTC QLQ-C30 is a 30-item questionary, the content areas covered by the questionnaire reflect the multi-dimensionality of the QoL construct. If we focus in any specific item of the QLQ-C30 scale (a total of 30 items/questions), it can be seen that there are two different types of questions[18]:

- From question 1 to 28, the questions have four ordinal responses (Not at all", "A little", "Quite a bit" and "Very much")

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

- Questions 29-30 have discrete scale from 1 to 7 (very poor to excellent)

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Some of the 30 questions are combined to create scales (a scale is a combination of different questions). Consequently, the 30 questions of the QLQ-C30 are transformed in 15 different scales. There are three different types of scales.

- One global health status/ QoL scale
- Five functional scales
- Nine symptom scales

In the next table it can be visualized the name of the scales, the number of questions/items that include each scale, the item range and the QLQ-C30 questions that contribute in the calculation of each scale[18].

Table 1 : Relation between scales and items in the EORTC QLQ-C30 questionnaire

	Number of items	Item range*	Item numbers
Global health status / QoL			
• Global health status/QoL	2	6	29,30
Functional scales			
• Physical functioning	5	3	1 to 5
• Role functioning	2	3	6,7
• Emotional functioning	4	3	21 to 24
• Cognitive functioning	2	3	20,25
• Social functioning	2	3	26,27
Symptom scales			
• Fatigue	3	3	10,12,18
• Nausea and vomiting	2	3	14,15
• Pain	2	3	9,19
• Dyspnoea	1	3	8
• Insomnia	1	3	11
• Appetite loss	1	3	13
• Constipation	1	3	16
• Diarrhoea	1	3	17
• Financial difficulties	1	3	28

*Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3.

First, we will formally define how to calculate the score values and then, we will try to facilitate the interpretation with a practical example. Having 30 items ($I_1, I_2, \ldots I_{30}$), the principle for scoring all the scales is the following:

1) Estimate the mean of the item values that contribute to the scale; this is the raw score. If items $I_1, I_2, \ldots I_n$ are included in a scale, the procedure is as follows:

$$Raw\ score = RS = (I_1 + I_2 + .. + I_n)/n$$

2) Use a linear transformation to standardise the raw score, so that scores range from 0 to 100. Apply the linear transformation to 0-100 to obtain the score S:

$$Global\ health\ status\ /\ QoL: \quad S = \left\{\frac{(RS-1)}{range}\right\} x\ 100$$

$$Functional\ scales: \quad S = \left\{1 - \frac{(RS-1)}{range}\right\} x\ 100$$

$$Symptom\ scales\ /\ items: \quad S = \left\{\frac{(RS-1)}{range}\right\} x\ 100$$

Range is the difference between the maximum possible value of RS and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. As mentioned previously, most items are scored 1 to 4 (range = 3). The exceptions are the items contributing to the global health status / QoL, which are 7-point questions (range = 6).

Using a practical example, if we want to calculate the score of the *emotional functioning* scale:

$$Raw\ score = RS = (I_{21} + I_{22} + I_{23} + I_{24})/4$$

$$Emotional\ functioning\ score = \left\{1 - \frac{(RS-1)}{3}\right\} x\ 100$$

If the patient punctuations for the emotional scale are the following:

During the past week:	Not at All	A Little	Quite a Bit	Very Much
21. Did you feel tense?	1	(2)	3	4
22. Did you worry?	1	2	(3)	4
23. Did you feel irritable?	1	2	(3)	4
24. Did you feel depressed?	1	(2)	3	4

$$Raw\ score = RS = \frac{2+3+3+2}{4} = 2.5$$

$$Emotional\ functioning\ score = \left\{1 - \frac{(2.5-1)}{3}\right\} x\ 100 = \mathbf{50}$$

The final score of emotional functioning will be 50. The same calculations will be used for the other scales.

2.3 Scaling scores

The majority of HRQoL scores use scaling techniques to calculate the final score (e.g., the EORTC QLQ-C30 scale values from 0 to 100)[18]. The scaling techniques are based upon the widely applied Likert method of summated scales, in which the constituent items within each scale are simply summed. However, those techniques make some assumptions 1) give equal weight to each item and 2) each item is graded on a linear or equal-interval scale. Some criticism can appear for the using of the scaling techniques, but following the principle of parsimony, it has been accepted that "*simple integer scoring is likely to be enough for many purposes*"[19]. For that reason, the EORTC Quality of Life Group is currently recommending the use of scales based upon unweighted summed scores and assuming the adequacy of linear scores[18].

In fact, the main disadvantage in the use of transforming scores is the difficulty in the interpretation of the results. It is unknown if a change in 10-units in a scale from 0 to 100 is clinically relevant. And this interpretation is even more challenging when the objective of the analysis is to study the change in scores over time. The fact that a change is statistically significant does not necessarily imply that it also has clinical significance. The use of raw scores along with a proper graphical representation can be a help in results interpretation.

3. Statistical modelling

HRQoL assessment is used as an outcome measure to objectively analyse the patient's reported quality of life. However, there is little consensus about the analysis, interpretation, and reporting of these data from a statistical perspective[7] [8].

The data collected in HRQoL is quite heterogeneous due to the following four reasons: 1) it combines numerical and ordinal questions, 2) it combines multidimensional data with different subscales to characterise patients' symptoms and functioning, 3) it has to take into account longitudinal assessments over time that require repeated measurements and 4) it might have missing data because some patients did not complete all the study follow-up. To face this complex data, different statistical approaches can to be used to answer different questions. However, the use of inappropriate statistical methods could bias the findings and let to incorrect conclusions[7].

The Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data for Cancer Clinical Trials (SISAQOL) consortium undertook in 2018 a systematic literature review to describe the most used statistical methods to analyse PROs in randomized controlled trials in metastatic breast cancer[7]. Additionally, Arostegui et al (2012) discussed previously some statistical approaches to analyse PROs[20]. In what follows we describe the most used statistical approaches in this setting:

3.1 Linear model

The linear model is one of the most used techniques to analyse HRQoL data. The model assumes a linear relation between the dependent and the independent variable plus a random error component. This model assumes that the observed score Y is a continuous variable. Then, $Y_1, \dots, Y_n$ are independent and continuous random variables that represent the response of the ith subject.

$$Y_i = \beta_0 + \beta_1 * X_i + \varepsilon_i$$

where $E(\varepsilon_i) = 0, \ \ var(\varepsilon_i) = \sigma^2$ and $i = 1, \dots, n$.

The parameters β_0 and β_1 are the regression coefficients (β_0 $intercept$, β_1 $slope$). In this specific case, Y_i is the HRQoL score for each patient in each evaluation, X_i is the treatment indicator (in randomized studies 0 if patient receive the control treatment and 1 for the experimental treatment) and β_1 is the coefficient associated with the treatment indicator. If β_1 is statistically different to 0, the study can conclude that the HRQoL scores are different between treatment arms. And, consequently, one treatment is associated with better patient's quality of life than the other. The model estimation is usually performed by means of the least squares method or with the bootstrap estimation.

However, the linear model assumes that the observations are independent between each other's. As we mentioned previously, PROs outcomes are usually collected in a longitudinal assessment and each patient provides several scores at different time points. This method does not take into consideration the intra patient

variability and yields a biased estimation. In the R statistical software, the most used function to estimate linear models is *lm* (package *stats*).

3.2 Tobit regression

The Tobit model assumes that the response variable Y is normally distributed, but only values in a given interval can be observed (the model is known as the censored normal distribution model). Consequently, the Tobit model can be used when the response variable is observed in the $[a, b]$ interval[20].

$$Y_i^{to} = \beta_0 + \beta_1 * X_i + \varepsilon_i$$

with

$$Y_i = \begin{cases} a, & if \;\; y_i^{to} \leq a \\ y_i^{to}, & if \; a < \; y_i^{to} < b, \quad i = 1, \dots, N \\ b & if \;\; y_i^{to} \geq b \end{cases}$$

where $a, b \in R$ with $a < b$, and the ε_i is assumed to be independent normally distributed random variables with mean zero and constant variance, $\varepsilon_i \sim N(0, \sigma^2), \; i = 1, \dots, N$.

As observed in section 2.2 with the explanation of the EORTC QLQ-C30 questionary, the observed scores are restricted to the [0,100] interval. In this case the log-likelihood function can be written as[20]:

$$l(\beta, \sigma; y) = \sum_{i \in \{0 < y_i < 100\}} \left(\frac{1}{\sigma}\right) ln\emptyset\left(\frac{Y_i - (\beta_0 + \beta_1 * X_i)}{\sigma}\right)$$
$$+ \sum_{i \in \{y_i = 100\}} ln\Phi\left(-\frac{100 - (\beta_0 + \beta_1 * X_i)}{\sigma}\right) + \sum_{i \in \{y_i = 0\}} ln\Phi\left(\frac{-(\beta_0 + \beta_1 * X_i)}{\sigma}\right)$$

where $\emptyset$ and Φ are the standard normal cumulative distribution and probability density functions, respectively.
In the R statistical software, the most used function to estimate the Tobit model is *vglm* (package *VGAM*).

3.3 Linear and generalized linear mixed model

Linear mixed model

An extension of the linear regression is the linear mixed model where fixed and random effects are combined. In the linear mixed model, it is assumed that the dependent variable (HRQoL scores) is normally distributed. The most important change is the introduction of random effects in the model estimation (in this case, individuals' effects). Consequently, the effects of the subjects are treated, but without being parameters of the model. Linear mixed models are usually estimated via Newton-Raphson method and the model does not loss degrees of freedom to estimate random effects. The formal formulation of this model is as follows[21]:

$$Y_{ij} = (\beta_0 + b_{i0}) + (\beta_1 + b_{i1}) * X_{ij} + \varepsilon_i$$

where $\tilde{b}_{i0} = (\beta_0 + b_{i0})$ and $\tilde{b}_{i1} = (\beta_1 + b_{i1})$. β is a vector of population-average regression coefficients (fixed effects) and b_i is a vector of subject-specific regression coefficients (random effects). b_i is assumed to be $b_i \sim N(0, \alpha^2_{ind})$ and describes how the evolution of the ith subject deviates from the average evolution in the population. j corresponds with the observation number in each individual. The residual distribution is $\varepsilon_i \sim N(0, \alpha^2_{res})$.

The mixed model implies a specific correlation structure:

- Observations from different subjects are independent
- Observations within subjects are positively correlated

Different formulations in the linear mixed model are possible depending on whether random effects are included in the intercept and/or in the slope.

- Model 1: Model with no random effects ($b_0 = b_1 = 0$)
- Model 2: Model with random intercept ($b_0 \neq 0,\ b_1 = 0$)
- Model 3: Model with random slope ($b_0 \neq 0,\ b_1 = 0$)
- Model 4: Model with random intercept and slope but not correlation ($b_0 \neq 0,\ b_1 \neq 0,\ \text{cor}(b_0, b_1) \approx 0$)
- Model 5: Model with random intercept and slope and correlation ($b_0 \neq 0,\ b_1 \neq 0, |\text{cor}(b_0, b_1)| > 0$)

In the R statistical software, the most used functions to estimate linear mixed models are *lme* (from the package *nlme*) and *lmer* (package *lme4*).

However, a Bayesian approach can be also used to formulate the linear mixed model. Assuming that b_i random effects are random values, the model can be formulated with b_i with a normal prior distribution with mean 0.

$$Y_i | b_i \sim N(X_i * \beta + Z_i * b_i, \sum i)$$

$$where\ the\ prior\ distribution\ of\ b_i\ is: \quad b_i \sim N(0, D)$$

Generalized linear mixed model

Generalised linear mixed model (GLMM) follow the same structure that the linear mixed models but now the model assumes that the dependent variable is non-normally distributed. The most used distributions for GLMM are binomial, poisson and gamma.

Random effects follow a normal distribution and can be used to generate an association structure between repeated measurements. The random effects can be included in the intercept to allow for a patient-specific baseline estimation or/and in the slope to allow a patient-specific estimation of the evolution over time. However, the

interpretation of the fixed parameters is the same than in the linear model. In the R statistical software, the most used functions to estimate GLMM is *glmer* (package *lme4*) although some specific functions are available to fit specific types of distributions (R function *glmer.nb* for fitting negative binomial distribution).

3.4 Beta-binomial approach

Another approach to analyse HRQoL data is the use of the beta-binomial distribution. This distribution could be recommended when the outcome of interest has a skewed distribution or in outcomes that are measured on an ordinal scale. The beta-binomial distribution consists of a finite sum of Bernoulli-dependent variables whose probability parameter is random and follows a beta distribution[22]. On one hand, it is assumed that Y_1,..., Y_m are independent and follow a Bernoulli distribution with parameter u, after conditioned on a random variable u. On the other hand, the probability parameter (u) follows a beta-distribution with parameters α_1 and α_1.

$$Y_i | \, u \sim Bernoulli(u) \quad and \quad u \sim Beta(\alpha_1 \, , \alpha_2)$$

If we sum up all the variables, we will define a new variable:

$$Y = \sum_{i=1}^{m} y_i$$

This variable will follow a beta-binomial distribution with:

$$Y | \, u \sim Bin(m, u) \quad and \quad u \sim Beta(\alpha_1 \, , \alpha_2)$$

The beta-binomial distribution does not belong to the exponential family and, consequently, the estimation in the regression context is not simple. Two different approaches have been defined to estimate the beta-binomial regression i) beta-binomial distribution with the logistic link or ii) hierarchical generalized liner models[22].

Beta-binomial regression

Considering a beta-binomial distribution of a maximum score of m, and a set of response variables Y_1,..., Y_n.We can use the following reparameterization $\alpha_{1i} = \frac{p_i}{\emptyset}$ and $\alpha_{2i} = \frac{(1-p_i)}{\emptyset}$. Then[22]:

$$E[y_i] = mp_i \qquad and \qquad Var[y_i] = mp_i \, (1 - p_i \,) \; [1 + (m - 1) \frac{\emptyset}{1+\emptyset}]$$

Consequently, it is possible to interpret the beta-binomial distribution as a binomial distribution with some over-dispersion structure which is given by the intraclass correlation through the summed Bernoulli observations. Therefore, the interpretation is similar to the binomial case, where p_i is the probability of success in each Bernoulli observation of the individual i.

Moreover, assuming that the probability parameter p_i is connected to a vector of regression parameters by means of a logit link function model, it is possible to formulate the following relationship between the probability parameter of the beta-binomial distribution of each individual and some given covariates (X_1,..., X_t).

$$p_i = \exp(x_i'\beta) / (1 + \exp(x_i'\beta))$$

And then:

$$\log\left(\frac{p_i}{1 - p_i}\right) = x_i'\beta$$

Hierarchical generalized linear model approach

The hierarchical generalized linear model (HGLM) approach differs from the generalized linear mixed model (GLMM) in the following detail: while GLMM have one or more normal random effects, HGLM use non-normally distributed random effects. Consequently, we could understand the HGLM as a GLMM model that use non-normally distributed random effects. The distribution of random components is extended to conjugates of arbitrary distribution from the GLM family.

The HGLMs are defined in two parts. First, the response variable *Y*, conditional on some given random components u, follows a GLM family:

$$\mathrm{E}[\mathrm{Y}|\mu] = \mu \qquad \text{and} \qquad \mathrm{Var}[\mathrm{Y}|\mu] = \lambda \mathrm{V}(\mu)$$

Where the linear predictor takes the form:

$$\mathrm{g}(\mu) = \mathrm{X}\beta + \mathrm{Z}\mathrm{v} \qquad \text{where } \mathrm{v} = \mathrm{v}(\mu) \text{ is the random effect and } \beta \text{ the fixed effect}$$

Second, the random components μ follow a distribution conjugate to a GLM family of distributions with parameter ∅. Due to the fact that the beta distribution is conjugate to the binomial GLM, we can consider the beta-binomial model as a special case of the HGLM family, where:

$$y_i \mid u_i \sim Bin(m, p_i) \quad and \quad u_i \sim Beta(\alpha_1, \alpha_2)$$

And the linear predictor of the beta-binomial HGLM is

$$\log(p_i) = x_i'\beta + v_i$$

The main differences between both estimation approaches is that the beta-binomial regression has a population-average interpretation while the HGLM has a subject specific interpretation. Although the interpretation of the fixed part regression coefficients β in both models is equivalent to the log odds-ratio in a binomial logistic

regression model. Najera-Zuloaga et al[22] conducted a simulation study to compare both estimation and they reached the conclusion that beta-binomial regression obtained more precise estimation specially when the dispersion parameter increases.

In the R statistical software, the function that performs the logistic regression based on a beta-binomial distribution is the *BBreg* function (*PROreg* package) and for the HGLM approach the function with the same name *hglm* can be used (*hglm* package).

Beta-binomial mixed-effects model for longitudinal data

Until now we have studied the beta-binomial distribution in a cross-sectional framework. In other words, when the study data comes from a unique and specific time-point. However, the methodology can be extended to deal with longitudinal data[23]. In this section, we will describe a beta-binomial mixed-effects model that incorporates a normally distributed random effect in the linear predictor. This extension is built under the marginal approach (as we have already mentioned, the beta-binomial regression has a population-average interpretation and can be interpreted as a marginal approach).

As we described previously, $Y_1,\ldots, Y_n$ are assumed to be independent and follow a beta-binomial distribution after conditioning on the random effect u. Now, we assume that u follows a multivariate normal distribution with zero mean and variance–covariance matrix $\mathbf{D}$, which depends on a vector of variance parameters λ.

$$y_i \mid u \sim Beta - binomial(m_i, p_i, \emptyset) \qquad and \qquad u \sim N(0, D(\lambda)) \quad , \text{i=1,....,n}$$

We introduce the parameter vector $\theta = (\phi, \lambda)$, to incorporate all the dispersion components of the model. Under the marginal beta-binomial regression approach, we can link the probability parameter of the beta-binomial distribution with i) the X covariates and ii) the random effects that are defined to be fixed.

$$\log\left(\frac{p_i}{1-p_i}\right) = x_i'\beta + z_i'u\,, \quad i = 1, \ldots, n$$

Where p_i is the probability parameter of the beta-binomial distribution, β are the fixed effects, u is the random effects vector (length q) and z_i' is the ith row of the $n * q$ model matrix Z composed by the random structure of the model. Additionally, as defined in the linear mixed model section, the model can include random effects in the intercept and/or in the slope. More details about the model estimation can be obtained in the publication "*A beta-binomial mixed-effects model approach for analysing longitudinal discrete and bounded outcomes*"[23].

In practical terms, the beta-binomial mixed-effects model estimation to fit longitudinal data can be obtained with the R function *BBmm* (R package *PROreg*).

3.5 Multiple pairwise comparison

Another statistical approach is to compare the quality of life scores in each specific time-point rather than the changes in scores over time. To compare the quality of life scores between the two study groups in any specific time point, the most used methods are i) the t-test and ii) the Wilcoxon rank-sum test. Those tests asses if there is enough evidence to reject the null hypothesis that the two independent samples came from the same population.

The T-test is based on the Student's t-distribution developed by the statistician William Sealy Gosset (worker of the Guinness brewery) under the pseudonym of Student[24]. This distribution applies where the response follows a normal distribution, but the standard deviation (σ) is unknown and has to be estimated (s).

$$t = \frac{\bar{X}_n - \mu}{s/\sqrt{n}} \sim t_{n-1}$$

where $\bar{X}_n$ is the sample mean and μ the expected mean. To build the confidence interval with a certain probability $(1-\alpha)$ we can apply the formula below:

$$P\left(-t_{n-1} * \frac{\alpha}{2} \leq \frac{\bar{X}_n - \mu}{s/\sqrt{n}} \leq t_{n-1} * \frac{\alpha}{2}\right) = 1 - \alpha$$

In our case, the aim is to compare the scores of two independent populations (treatment arms). Assuming that $\bar{x}_1$ is the sample mean score in the control group, $\bar{x}_2$ the sample mean in the experimental group, n_1 the sample size in the control population and n_2 the sample size in the experimental population. Then:

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{s^2(\frac{1}{n_1} + \frac{1}{n_2})}}$$

$$s^2 = \frac{\sum_{i=1}^{n_1}(x_i - \bar{x}_1)^2 + \sum_{j=1}^{n_2}(x_j - \bar{x}_2)^2}{n_1 + n_2 - 2}$$

The Wilcoxon rank-sum test is the non-parametric version of the t-test.

To calculate the Wilcoxon rank-sum test[24], all observed values are sorted in an ascending manner and the observed values are transformed in ranges regarding its position (range 1 to the smallest value, range 2 to the second smallest value, etc.). Then, the sum of the ranges of the values in the control group will be R_c and the R_e for the values of the experimental arm. If the control group has n_1 observations and the experimental group n_2 observations ($N = n_1 + n_2$). Assuming that distributions in the control and experimental group are identical and independently distributed then:

$$E(R_c) = n_1 * \frac{(N+1)}{2}$$

$$Var(R_c) = \frac{n_1 * m}{12}(N+1)$$

while R_c is approximately normally distributed if the sample size is not very small ($n, m > 5$). The main advantage of the Wilcoxon rank-sum test over the Student t-test is that it doen not need assume that the response variable is normally distributed.

Those statistical methods do not allow to consider the longitudinal nature of the quality of life data. The comparison is performed in each time of evaluation, considering that the scores in each assessment are independent between each other's. Moreover, this methodology needs to adjust for multiple testing (not needed if a statistical technique that took into account the repeated measurements is used). The adjustment for multiple testing can lead to a decrease in the statistical power of the analysis. To avoid this issue, an alternative is to analyse only one time-point but this decision is arbitrary and, again, do not allow to consider all follow-up information.

3.6 Time-to-event analysis

The last approach to analyze HRQoL data is to use a time-to-event analysis. To use this approach, the *event* of health-deterioration has to be defined (e.g at least 10-points diminution of the HRQoL score comparing with the baseline measurement). Once the event of health deterioration is clear, the study can assess in which group there is a higher risk to observe the event. The standard Cox model is commonly used in this situation.

The Cox model is a semi-parametric regression model used to study time-event variables. The model is divided into two functions i) the baseline function $h_o(t)$ and ii) an exponential function e^{BX}:

$$h(t,X) = h\,(t, X_1, \dots, X_P) = h_0(t)\exp\left(\sum_{j=1}^{p}\beta_j X_j\right)$$

On one hand, the baseline function corresponds with the risk of the reference individual (individual with 0 values in all the predictors covariates). It is the only part of the Cox model that is time-dependent. On the other hand, the exponential function is composed by non-time dependent covariates (e.g., allocated treatment).

The Cox model has become the most used methodology in the field of survival analysis. There are several reasons for this popularity: i) the baseline function $h_o(t)$ is not needed to estimate the regression coefficients (neither to estimate the hazard ratio (HR)), ii) being a semi-parametric model it is not needed to make assumptions about the statistical distribution of the study data (e.g;, Weibull, Exponential, etc.). Consequently, it is a robust alternative when there is some uncertainty with the correct fitting of data distribution[25].

The estimation method to obtain the model coefficients is the maximum partial likelihood estimation. The hypothesis test ($H_0: B_j = 0 \;\; vs \;\; H_0: B_j \neq 0$) can be made with the Wald test, the likelihood ratio statistic or

the log-rank test. All of them estimate the statistics under the idea that the null hypothesis follows a X^2 with p degrees of freedom (p =number of covariates).

Another important element in the Cox model is the hazard ratio (HR). The HR is defined as the division of the risk of two different individuals with different covariates.

$$HR = \frac{h(t,X^*)}{h(t,X)} = \frac{\widehat{h_0}(t) * e^{\sum_{i=1}^{p} \widehat{B_i} X_i{}^*}}{\widehat{h_0}(t) * e^{\sum_{i=1}^{p} \widehat{B_i} X_i}} = \frac{e^{\sum_{i=1}^{p} \widehat{B_i} X_i{}^*}}{e^{\sum_{i=1}^{p} \widehat{B_i} X_i}} = e^{\sum_{i=1}^{p} \widehat{B_i} (X_i{}^* - X_i)}$$

$$HR = e^{\sum_{i=1}^{p} \widehat{B_i} (X_i{}^* - X_i)}$$

In the specific situation where the individuals are only different in one unit of that covariate of interest (in our case: 0 control treatment, 1 experimental treatment), the formula can be simplified to:

$$HR = e^{\widehat{B_i}}$$

The 95% confidence interval (CI95%) is given by:

$$95\%\ CI\ HR = e^{(\widehat{B_i} + 1.96 * \sqrt{var(\widehat{B_i})})}$$

In the analysis of HRQoL data, Cox model extension as the inclusion of time-dependent covariates in the model is not used because all *Xs* covariates are defined at baseline and they do not change over the time. Other extensions as competing-risk analysis or the use of frailty models are not used for the nature of the study data. In the R statistical software, the most used functions to estimate standard Cox model is *coxph* (package *survival*).

3.7 Missing data

Missing data is a common problem in HRQoL data. Events such as death, treatment discontinuation, or study discontinuation (due to disease progression or poor treatment response) usually affects the collection of quality of life data and in practical terms to obtain complete data is almost impossible[26].

Missing data could be observed in a single item (different items are defined within a questionnaire), or the whole questionnaire could be missing for a subject. In theory, it is important to distinguish between items, which are accidentally missing, and items, which are missing for a particular reason. However, it is likely to not have any evidence to decide whether there was a specific reason for the missing values.

From a statistical perspective, three different types of missing data can be defined 1) missing completely at random (MCAR), 2) missing at random (MAR) and 3) missing not at random (MNAR). To understand the different types of missing data, we define the following notation[21]:

Subject i has a response in different time-points (j). The response variable is Y_{ij}

$$Missingness\ indicator \quad R_{ij} = \begin{cases} 1 & if\ Y_{ij}\ is\ observed, \\ 0 & otherwise \end{cases}$$

We can separate Y_{ij} in two vectors:

$$\begin{cases} Y_i^o & contains\ Y_{ij}\ for\ which\ R_{ij} = 1 \\ Y_i^m & contains\ Y_{ij}\ for\ which\ R_{ij} = 0 \end{cases}$$

$$D_i: time\ of\ dropout:\ D_i = 1 + \sum_{j=1}^{n_i} R_{ij}$$

Statistical modelling begins by considering the full data density:

$$f(Y_i, D_i | X_i, \theta, \psi)$$

where X_i is the design matrix for fixed effects, Y_i the response variable, D_i the time of droput and θ and ψ are vectors that parameterize the joint distribution. This formulation can be factorized in the following[21]:

$$f(Y_i | X_i, \theta)\ \boldsymbol{f(D_i | X_i, Y_i^o, Y_i^m, \psi)}$$

However, the right part of the formulation can be simplified based on the type of missing data:

- **Missing completely at random (MCAR)**: This is a particular case of missing where the decision to be on missing depends only on the covariates (not in the specific value of the response variable). Then:

$$f(Y_i \mid X_i, \theta)\, f(D_i \mid X_i, \psi)$$

To deal with it, two alternatives can be used:

  - Use only complete cases. The observed data will be an unbiased representation of the complete real data. The only problem is the reduction of the sample size that led to a decrement in statistical power and a wider confidence interval estimation.
  - Imputations following the last observed values (patient's previous responses to the same item) or to impute the mean value of the observed data The main advantage of using imputation compared to using only complete cases is the increment of the statistical power. The main disadvantage is that the study data will be composed by observed and estimated values.

- **Missing at random (MAR):** In this case the missing values depend on the covariates and in the observed responses (Y_i^o), Consequently:

$$f(Y_i \mid X_i, \theta)\, f(D_i \mid X_i, Y_i^o, \psi)$$

In this case, different techniques can be used to deal with missing data: multiple imputation, generalized estimated equations (GEE) or direct likelihood can be used to estimate the most likely value given information about (a) that patient's previous responses to the same item, (b) other patients' responses at a similar stage in their disease progression and therapy, or (c) the inter-relations and covariance structure with other items.

- **Missing not at random (MNAR):** This is the most problematic case of missing data because the missing values depends as well on the non-observed response values (Y_i^m). And this response value will never be observed:

$$f(Y_i \mid X_i, \theta)\, f(D_i \mid X_i, Y_i^o, Y_i^m, \psi)$$

Sensitivity analysis assuming different scenarios or the use of joint modelling could be a reasonable strategy.

In HRQoL analysis, in practice, one of the most common and simple method for imputing items from multi-item scales is the following*: if at least half of the items from the scale have been answered, assume that the missing items have values equal to the average of those items which are present for that respondent. If not, all the set scale score is considered missing*[18]. Example:

During the past week:	Not at All	A Little	Quite a Bit	Very Much
21. Did you feel tense?	1	(2)	3	4
22. Did you worry?	1	2	(3)	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	(2)	3	4

$$Raw\ score = RS = \frac{2 + 3 + 2.33 + 2}{4} = 2.33$$

$$Emotional\ functioning\ score = \left\{1 - \frac{(2.33 - 1)}{3}\right\} x\ 100 = \mathbf{55.6}$$

However, this rule is not always appropriate and an exercise to understand the magnitude of missing data in the study dataset has to be done. A major advantage of imputation is that, once the values have been filled in, standard complete data methods of analysis can be used.

4. Coralleen trial

4.1 Trial design and first efficacy results

The Coralleen trial is a randomised phase II study (NCT03248427) that aimed to compare i) neoadjuvant poli-chemotherapy and ii) letrozole plus ribociclib (L+R) treatment in women with hormone receptor-positive, HER2-negative, Luminal B breast cancer. Letrozole (L) is an endocrine therapy and ribociclib (R) is a cycling-dependent kinases 4 and 6 (CDK4/6) inhibition. The trial was designed with the hypothesis that endocrine therapy in combination with CDK4/6 inhibition (in this case L+R) could represent an alternative to multiagent chemotherapy in the study population.

As a study background, the CDK4/6 inhibitors (ribociclib is one of them) have proven to have meaningful therapeutic activity in metastatic breast cancer[27] [28] [29]. The combination of ribociclib with endocrine therapy (letrozole) have consistently demonstrated longer progression-free survival and overall survival over single agent (letrozole alone) and substantial equivalence with chemotherapy for the first- and second-line treatment of advanced disease[30] [31]. In the treatment of patients without metastasis, clinical and biological outcomes from clinical trials testing CDK 4/6 inhibitors have been divergent, likely due to discrepancy in the risk profile of the examined patient population[32] [33]. Thus far, no consensus on the use of CDK 4/6 inhibitors in the adjuvant setting has been achieved.

Chemotherapy is associated with increased toxicity burden in comparison with endocrine therapy, especially nausea, vomiting and alopecia[34]. Although endocrine therapy is recommended for some patients with breast cancer, chemotherapy is still strongly indicated in presence of features of lower endocrine responsiveness and/or high tumor burden[34] [35]. Luminal B breast cancer represents an unmet medical need given its lower sensibility to endocrine therapy[36]. It has been hypothesized that adding CDK 4/6 inhibitors (ribociclib) to standard endocrine therapy (letrozole) could increase the efficacy paving the possibility to avoid chemotherapy in patients with breast cancer but without metastasis. Many trial programs aiming to de-escalate the intensity of treatment in some low-risk patients using early putative biomarkers of response.

In the CORALLEEN study, a total of 106 postmenopausal women with stage I-IIIA HR+/HER2-negative Luminal B breast cancer were randomized 1:1 to receive i) six 28-days cycles of daily letrozole (2.5mg; continuous) and ribociclib (600mg; 3-weeks-on/-week-off) (n=52) or ii) four cycles of AC (doxorubicin 60mg/m2 and cyclophosphamide 600mg/m2 every 21 days) followed by weekly paclitaxel during 12 weeks (n=54). The primary efficacy endpoint was the proportion of patients with PAM50 Risk of Recurrence (ROR) low disease at surgery in each arm.

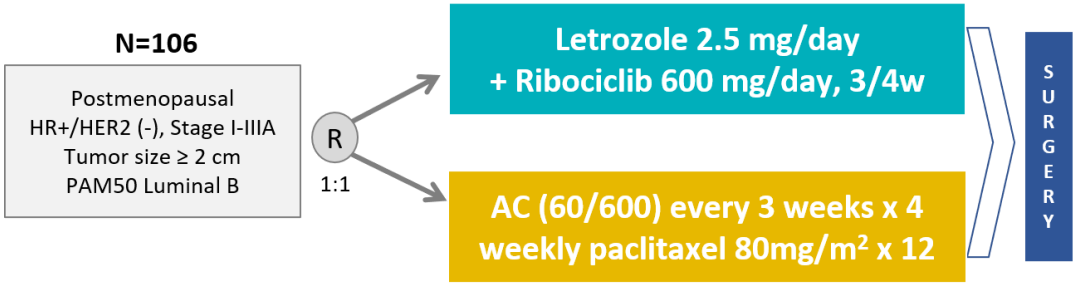


Figure 1: Coralleen trial design

In the primary efficacy analysis, both groups showed a similar proportion of patients with PAM50 low-risk risk of recurrence at surgery (46.9% vs. 46.1%)[9].

4.2 HRQoL questionnaires in the Coralleen trial

Another important objective of this study was to assess if avoiding chemotherapy, the patients could obtain a better quality of life during the treatment period. For this purpose, two questionnaires were used to evaluate patients-reported HRQoL at baseline, day 1 of each subsequent cycle, before surgery and at the end of the study:

- The European Organization for Research and Treatment of Cancer (**EORTC QLQ-C30**)
  - One global health status/ QoL scale
  - Five functional scales (physical, role, emotional, cognitive and social)
  - Nine symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and final difficulties)
- The breast cancer-specific **EORTC QLQ-BR23**
  - Four functional scales (body image, sexual functioning, sexual enjoyment and future perspective)
  - Four symptom scales (systematic therapy side effects, breast symptoms, arm symptoms and upset by hair loss)

As mentioned in the subsection 2.2, all the scales were transformed in scores from 0 to 100.

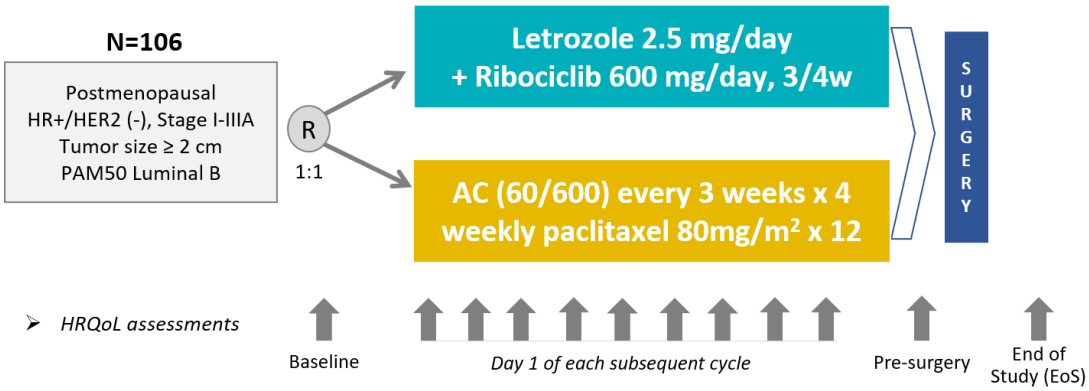


Figure 2: Coralleen trial design with health-related quality of life (HRQoL) assessments

The HRQoL scores were collected at different type points between study arms. On one hand, the cycle of L+R was administrated every 4 weeks and, consequently, the HRQoL evaluation for patients receiving L+R were collected every 4 weeks. On the other hand, CT cycles were administrated every 3 weeks and HRQoL evaluations were collected every 3 weeks in patients receiving chemotherapy.

However, the duration of the treatment is the same in both arms, 24 weeks from *baseline* to *pre-surgery* assessment (Figure 2). The last time-point where patients receive the treatment is at *pre-surgery*. The end of study (EoS) evaluation is a control evaluation three-months after surgery. Consequently, from pre-surgery evalution to the end of the study, patients did not receive the study treatment. The trial is interested in evaluating if HRQoL outcomes are different between treatment arms when patients receive the treatment (from baseline to pre-surgery). And to assess, if three months after surgery (EoS time-point), the HRQoL outcomes are similar to baseline levels.

5. Data analysis

5.1 Study dataset

The dataset with patient-reported outcomes (PROs) of the 106 patients included in the study Coralleen has a total of 1063 rows and 57 variables. Each row contains information of one patient evaluation. Consequently, if the patient (ID=1) has four visits, there will be four rows with information related to ID 1 patient. The number of variables corresponds with: i) four columns with visit information (Patient ID, treatment allocation, number of visit, day of visit), ii) the 30 questions from EORTC QLQ-C30 questionnaire, iii) the 23 questions from EORTC QLQ-BR23 questionnaire. In the figure below we can see a screenshoot with information for the first three patients (ID: 1001-001, 1001-002, 1003-004), treatment allocation, visit information and information of the first three items from the EORTC QLQ-C30 questionnaire.

ID.patient	Arm	Visita	Day.of.visit	QLQ-C30-Q1	QLQ-C30-Q2	QLQ-C30-Q3
1001-001	AC+pacli	0.Week1	2018-02-28	1	1	1
1001-001	AC+pacli	1.Week3	2018-03-21	1	1	1
1001-001	AC+pacli	2.Week6	2018-04-11	1	1	1
1001-001	AC+pacli	3.Week9	2018-05-03	1	1	1
1001-002	Letro+Ribo	0.Week1	2018-11-28	1	1	1
1001-002	Letro+Ribo	1.Week4	2018-12-26	1	1	1
1001-002	Letro+Ribo	2.Week8	2019-01-24	1	1	1
1001-002	Letro+Ribo	3.Week12	2019-02-22	1	1	1
1001-002	Letro+Ribo	4.Week16	2019-03-22	1	1	1
1001-002	Letro+Ribo	5.Week20	2019-04-16	1	1	1
1003-004	Letro+Ribo	0.Week1	2018-07-26	1	2	1
1003-004	Letro+Ribo	1.Week4	2018-08-23	1	1	1
1003-004	Letro+Ribo	3.Week12	2018-10-18	2	2	1
1003-004	Letro+Ribo	4.Week16	2018-11-15	1	1	1

As was mentioned in the section 4.2, the study treatments have a different schedule of visits and PROs were not collected at the same time points in patients receiving Letrozole plus Ribociclib (L+R) treatment and in patients receiving chemotherapy (CT) treatment. On one hand, the first patient (ID: 1001-001) received CT treatment (doxorubicin, cyclophosphamide and paclitaxel treatments) every 3 weeks and quality of life evaluations were collected every 3 weeks. On the other hand, the second and third patient (ID: 1001-002, 1003-004) received L+R treatment and had the quality-of-life evaluations every 4 weeks.

In the screenshot from the Coralleen trial dataset we can visualise the information regarding the first three questions in the EORTC QLQ-C30 questionnaire.

ID.patient	Arm	Visita	Day.of.visit	QLQ-C30-Q1	QLQ-C30-Q2	QLQ-C30-Q3
1001-001	AC+pacli	0.Week1	2018-02-28	1	1	1
1001-001	AC+pacli	1.Week3	2018-03-21	1	1	1
1001-001	AC+pacli	2.Week6	2018-04-11	1	1	1
1001-001	AC+pacli	3.Week9	2018-05-03	1	1	1
1001-002	Letro+Ribo	0.Week1	2018-11-28	1	1	1
1001-002	Letro+Ribo	1.Week4	2018-12-26	1	1	1
1001-002	Letro+Ribo	2.Week8	2019-01-24	1	1	1
1001-002	Letro+Ribo	3.Week12	2019-02-22	1	1	1
1001-002	Letro+Ribo	4.Week16	2019-03-22	1	1	1
1001-002	Letro+Ribo	5.Week20	2019-04-16	1	1	1
1003-004	Letro+Ribo	0.Week1	2018-07-26	1	2	1
1003-004	Letro+Ribo	1.Week4	2018-08-23	1	1	1
1003-004	Letro+Ribo	3.Week12	2018-10-18	2	2	1
1003-004	Letro+Ribo	4.Week16	2018-11-15	1	1	1

In the section 2.2 we have presented the meaning of those questions and the four possible responses (*1: Not at all, 2: A little, 3: Quite a bit, 4: Very much*).

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

Following the formulation presented in section 2.2, the individual questions will be combined to calculate a final score for each scale (global health status, functioning scales and symptom scales). From this point, we will work with scales values (as it has been explained in subsection 2.2, the scale is a combination of different questions) and we will not work with the value of individual items.

5.2 Baseline evaluation

Compliance rate at baseline evaluation

At baseline evaluation (week 1) not all included patients in the clinical trial completed PROs for health-related quality of life (HRQoL). Among the 106 patients included in the trial, the compliance rates of PROs at baseline for each scale can be visualized in Table 2 i) overall and ii) by treatment arm.

Table 2: Patient reported outcomes (PROs) compliance rate at baseline evaluation

	Overall (n=106)	L+R (n=52)	CT (n=54)
EORTC QLQ-C30			
Global health status / QoL			
• Global health status/QoL	98 (92.5%)	51 (98.1%)	47 (87%)
Functional scales			
• Physical functioning	100 (94.3%)	52 (100%)	48 (88.9%)
• Role functioning	100 (94.3%)	52 (100%)	48 (88.9%)
• Emotional functioning	98 (92.5%)	51 (98.1%)	47 (87%)
• Cognitive functioning	97 (91.5%)	50 (96.2%)	47 (87%)
• Social functioning	94 (88.7%)	47 (90.4%)	47 (87%)
Symptom scales			
• Fatigue	100 (94.3%)	52 (100%)	48 (88.9%)
• Nausea and vomiting	100 (94.3%)	52 (100%)	48 (88.9%)
• Pain	100 (94.3%)	52 (100%)	48 (88.9%)
• Dyspnoea	100 (94.3%)	52 (100%)	48 (88.9%)
• Insomnia	99 (93.4%)	51 (98.1%)	48 (88.9%)
• Appetite loss	100 (94.3%)	52 (100%)	48 (88.9%)
• Constipation	100 (94.3%)	52 (100%)	48 (88.9%)
• Diarrhoea	95 (89.6%)	48 (92.3%)	47 (87%)
• Financial difficulties	94 (88.7%)	47 (90.4%)	47 (87%)
EORTC QLQ-BR23			
Functional scales			
• Body image	98 (92.5%)	51 (98.1%)	47 (87%)
• Sexual functioning	89 (84.0%)	49 (94.2%)	40 (74.1%)
• Sexual enjoyment	52 (49.1%)	32 (61.5%)	20 (37%)
• Future perspective	98 (92.5%)	51 (98.1%)	47 (87%)
Symptom scales			
• Systematic therapy side effects	98 (92.5%)	51 (98.1%)	47 (87%)
• Breast symptoms	98 (92.5%)	51 (98.1%)	47 (87%)
• Arm symptoms	97 (91.5%)	51 (98.1%)	46 (85.2%)
• Upset by hair loss	37 (34.9%)	18 (34.6%)	19 (35.2%)

It can be observed that the overall compliance rate is higher than 90% in the majority of scales, with no relevant differences observed between treatment arm. Of note, there are some specific scales such as *sexual enjoyment* and *upset by hair loss* where the compliance rate were considerably low (49.1% and 34.9% respectively).

Baseline scores

In this section we will study the score punctuation of the scales at baseline. First, we will focus in the *Global health status* (GHS) score of the EORTC QLQ-C30 questionary. Following EORTC recommendations (see section 2.2), the score is presented in a 0-100 scale (Figure 3A) but we also presented the distribution of the score based on the initial scale (score from 0-14, Figure 3B). The score distribution is skewed to the right (higher values are associated with better HRQoL). Consequently, a large percentage of the included patients showed a good global health status at baseline.

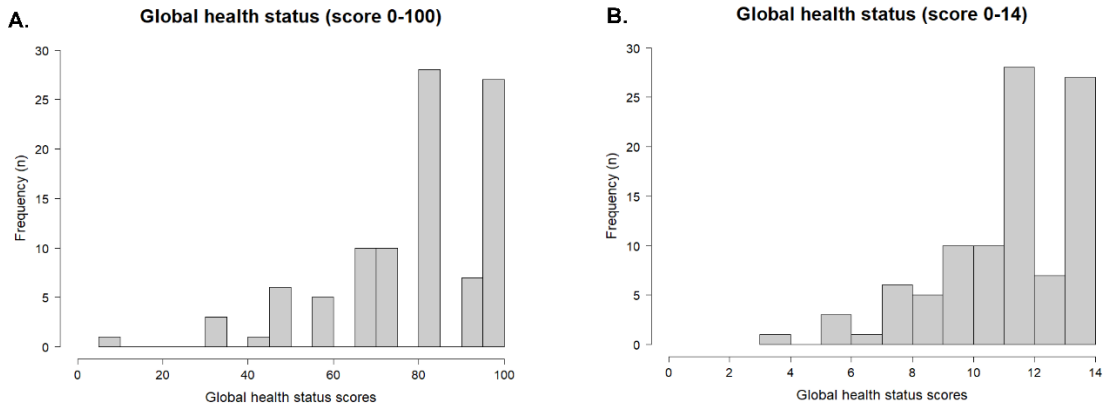


Figure 3: Histogram of *global health status* score at baseline in patients included in the Coralleen trial a) scaled score from 0 to 100, b) original score from 0 to 14.

As expected, there is no difference in GHS at baseline according to treatment arm (CT vs. L+R). At that moment, patients had not yet received the study treatment and no relevant differences are expected to be found in a randomised study. The mean score on the scaling scale (0-100) was 79.4 and 80.4 for patients treated with CT and L+R, respectively. In the original 0-14 scale, the mean score was 11.5 for patients receiving CT and 11.6 for patients receiving L+R (Figure 4).

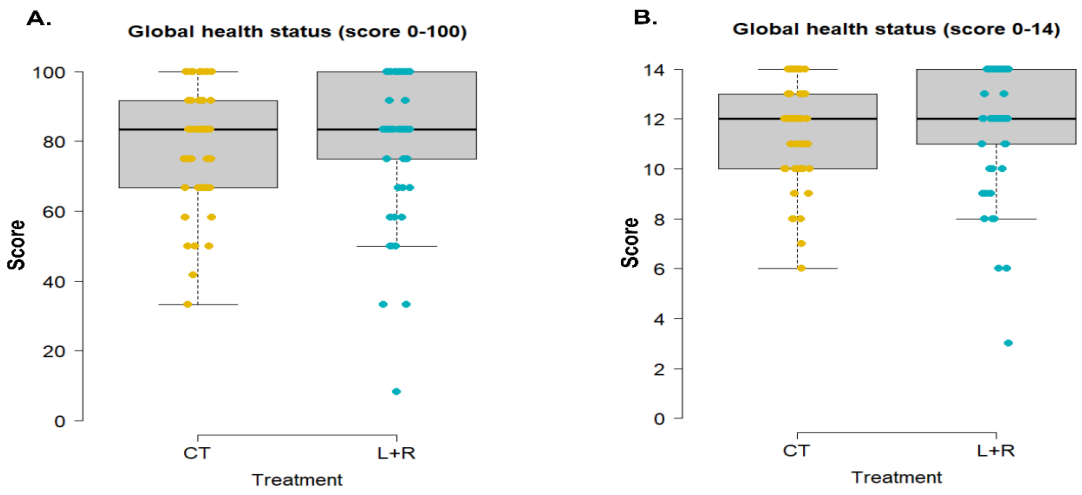


Figure 4: Boxplot with *global health status* score at baseline in patients included in the Coralleen trial per treatment arm a) scaled scores from 0 to 100 and b) original socres from 0 to 14.

Functioning scales at baseline

In functioning scales (EORTC QLQ-C30 and EORTC QLQ-BR23 questionaries) higher values are associated with better HRQoL. Overall, no relevant differences were found between treatment arms in any functioning scale at baseline (Figure 5).

However, the overall mean score was considerably heterogeneous across scales. On *physical, role, social* and *body image* scales the mean overall score was higher than 90 points (showing a good quality of life status in those outcomes). A reduction in the mean score was observed in the *cognitive scale* (89 points), *emotional scale* (72.6 points) and *future perspective* (62.6 points). The reduction was more relevant in sexual scales with a mean score of 29.5 points in *sexual enjoyment* and 14.8 points in *sexual functioning*. Figure 5 shows a radar chart with the mean score in each functioning scale per treatment arm. This is a graphical method to represent multivariate data (here functioning scales) in the form of a two-dimensional chart. All axes are joined in the center of the figure and the length of axes represents the mean of the scale.

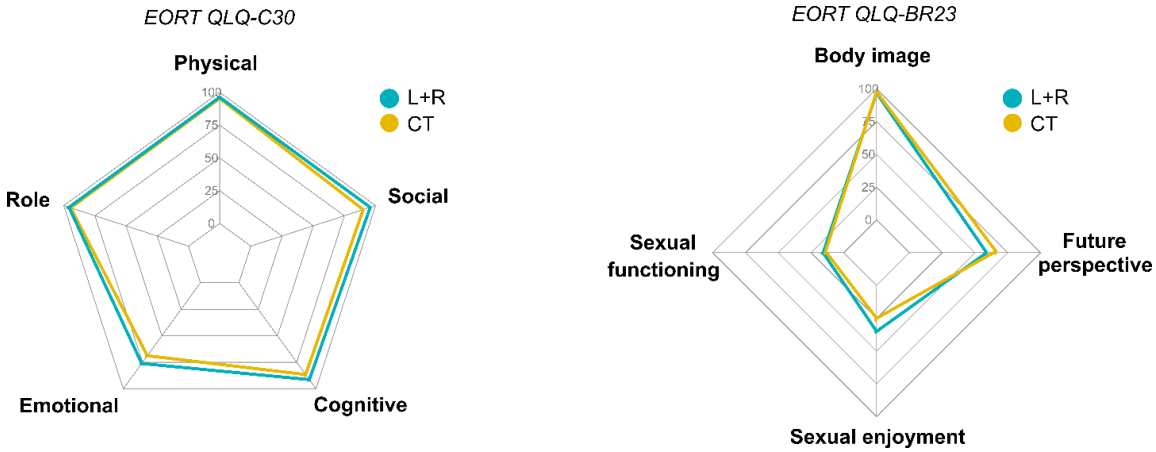


Figure 5: Radar chart with the mean score at baseline in functioning scales per treatment arm

Symptom scales at baseline

The interpretation of the symptom scales is different to functioning scales. Here, low values are associated with better HRQoL in symptom scales. Again, no difference was observed in symptom scales at baseline according treatment arms and a mean score of ≤ 20 points were observed in all scales.

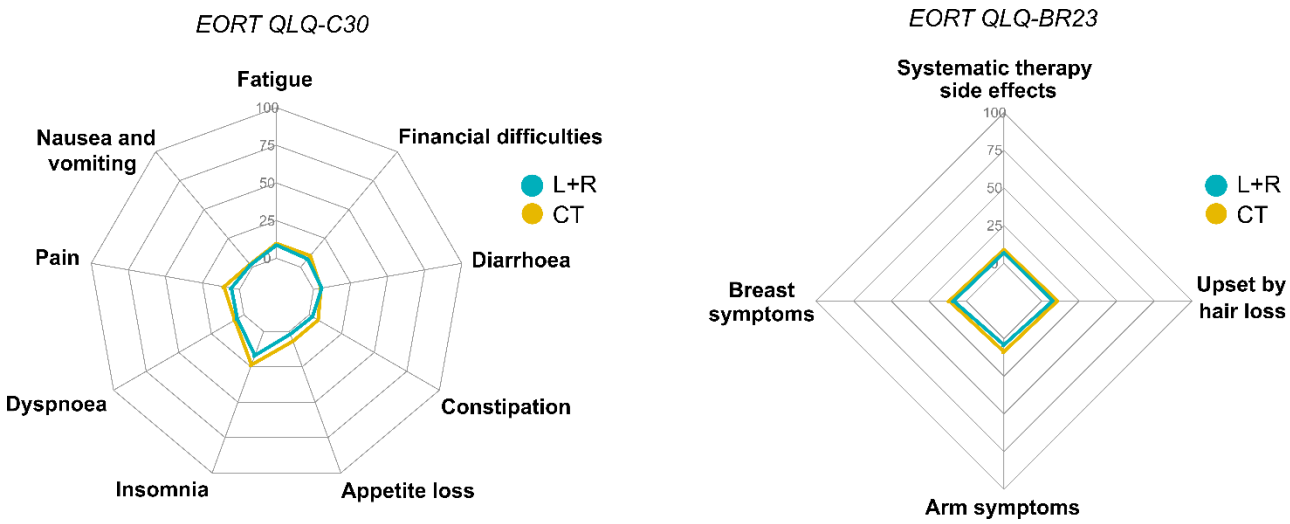


Figure 6: Radar chart with the mean score at baseline in symptom scales per treatment arm

5.3 Follow-up evaluations

Compliance rate during treatment administration

In section 5.2 we have already observed than more that 90% of patients included in the Coralleen trial fulfilled the patient-reported outcomes (PROs) to evaluate health-related quality of life (HRQoL) outcomes at baseline. It is as well relevant to take into account the PROs compliance rates during patient's follow-up. In the next table, we can observe the percentage of patients with available information in the *Global health status* scale in each time-point for patients receiving Letrozole plus Ribociclib (L+R).

Table 3: Patient reported outcomes (PROs) compliance rates at different time-points in patients with L+R treatment

Patients receiving L+R treatment (n=52)								
Time-point in weeks (w)	Baseline	4w	8w	12w	16w	20w	Pre-surgery	End of study
n of compliance (%)	51 (98.1%)	51 (98.1%)	49 (94.2%)	45 (86.5%)	46 (88.5%)	41 (78.8%)	38 (73.1%)	37 (71.2%)

At baseline, 51 out of 52 patients (98.1%) reported PROs information. At the pre-surgery (the last cycle of the treatment) a total of 73.1% of patients reported PROs. The same information is reported in Table 4 for

patients receiving CT treatment (n=54). Although in the first time-points the compliance rate was slightly lower than in the L+R group (87% vs. 98.1% at baseline and 88.9% vs. 98.1% at second evaluation), at the pre-surgery time-point the percentages were similar (73.1% vs. 74.1%). At the "*end of study*", the control evaluation three months after surgery, the compliance rates were 71.2% for L+R and 63% for CT.

Table 4: Patient reported outcomes (PROs) compliance rate at different time-points in patients with CT treatment

Patients receiving CT treatment (n=54)										
Time-point in weeks (w)	Baseline	3w	6w	9w	12w	15w	18w	21w	Pre-surgery	End of study
n of compliance (%)	47 (87%)	48 (88.9%)	48 (88.9%)	46 (85.2%)	44 (81.5%)	43 (79.6%)	41 (75.9%)	41 (75.9%)	40 (74.1%)	34 (63%)

For illustration purposes, the same information is reported graphically. From baseline to pre-surgery assessment the rate of compliance decreases progressively (Figure 7).

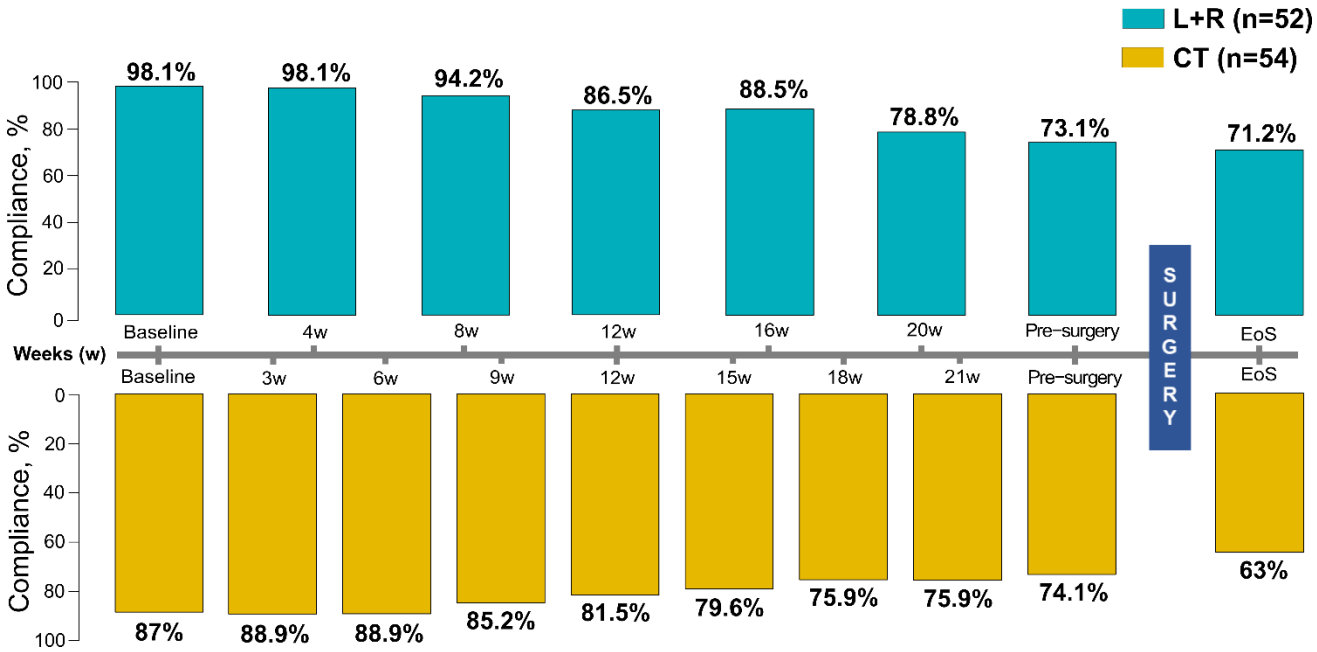


Figure 7: Compliance rate during study follow-up in patients receiving L+R and CT treatment

No data imputation will be performed in the primary data analysis and only observed information will be analysed.

5.4 Analysis of global health status

Previously, we have observed that HRQoL outcomes were similar between treatment arms at baseline assessment. In this section, we will study if HRQoL outcomes are different in patients receiving L+R or CT treatments during the study follow-up. For that purpose, we will use the statistical models defined in the section 3. The analysis has to be performed for each of the 23 scales independently (one global health status scale, 9 functioning scales and 13 symptom scales). Nevertheless, the same strategies will be applied in all the scales.

In this section we will only study the ***Global health status (GHS)*** scale of the EORTC QLQ-C30 questionnaire. To analyse the evolution of *GHS* scale three different strategies could be followed:

i) Study the **change value from the baseline** value

ii) Analyse the **absolute score** (in the 0-100 scale or in the original range scale)

iii) Study the **time to health-deterioration**.

Section 5.4 will be divided into four subsections. One subsection for each of the three strategies that can be used to study the *GHS* scale. In each subsection, different statistical methods will be used to deal with the nature and distribution of the data. The four and last subsection will be dedicated to analysis the impact of missing data.

In order to facilitate result interpretation, we have re-escalate the covariate *time*. As we have discussed in section 4.2, during the trial the treatment was administrated during 24 weeks (range 0-24 weeks). However, for data modeling we have re-escalate the range of the *time* to 0-1. Consequently, $time_i = 1$ is equivalent to pre-surgery time point (24 weeks) and $time_i$= 0.5 corresponds to week 12 of treatment.

5.4.1 Change from the baseline value

In some situations we could be particularly interested in studying the change from the baseline value. Especially if our main interest is to assess if HRQoL scores change in each patient during the treatment period independently of the initial value.

In Figure 8 we can observe the distribution of change from baseline values in the *global health status* scale at the second evaluation (week 3 for patients receiving CT and week 4 for patients receiving L+R) . Here the assumption of normally distributed values could be accepted.

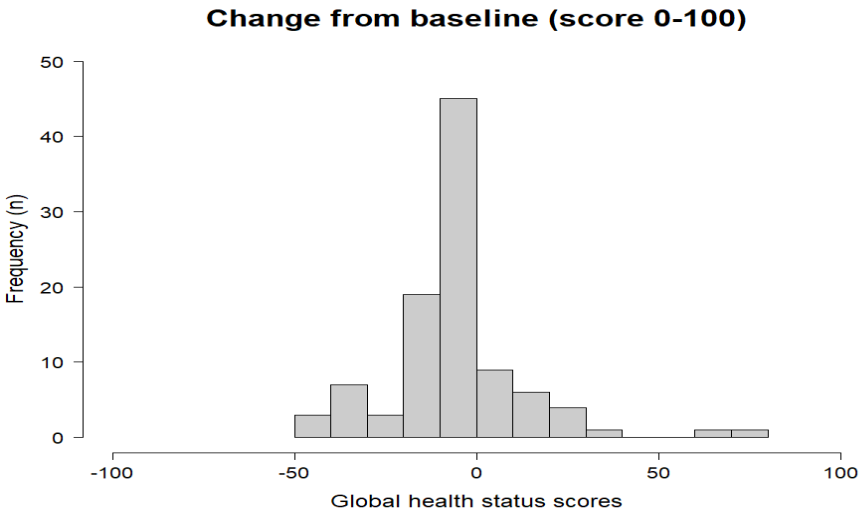


Figure 8: Histogram of the change from baseline values in *global health status* at second evaluation

In Figure 9 we depict the mean change from baseline score in the *global health status* (GHS) score per treatment arm in each evaluation time (or week) (along with the mean ± standard deviation). Note that 0 values represent no change from the baseline value. While a positive mean change from baseline is associated with an improvement of the GHS, a negative change is associated with a worsening in the quality of life. In the L+R group, GHS scores presented only a slight decrease from baseline to pre-surgery (week 24). However, GHS scores progressively decreased in the CL group.

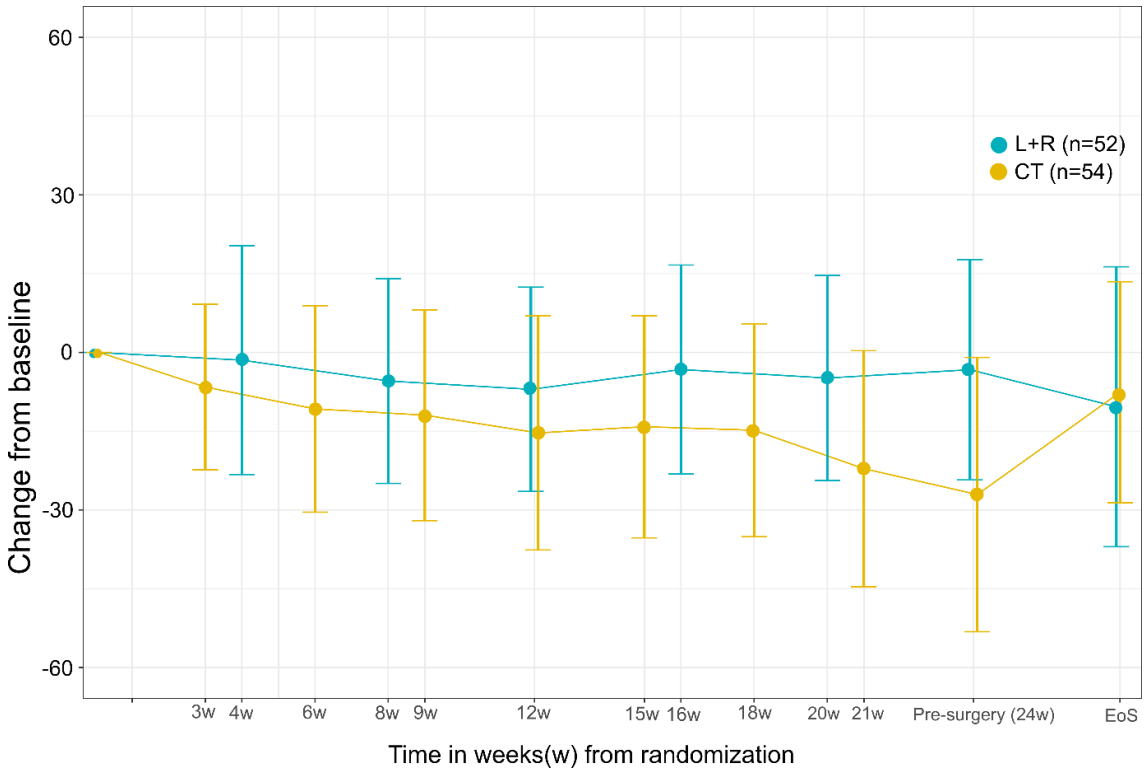


Figure 9: Evolution of the mean change from baseline values in *global health status* (along with the mean ± standard deviation) according treatment arm

To estimate the between-group difference in change from baseline, we will use three models: 1) **linear model**, 2) **Tobit regression** and 3) **linear mixed model.** One of the assumptions to use those models is that the response variable is approximately normally distributed.

The general equation for fitting the model incorporates two dependent variables and one interaction:

$$Change\ GHS_i = \beta_0 + \beta_1 * time_i + \beta_2 * Treat_i + \boldsymbol{\beta_3 * Treat_i * time_i} + \varepsilon_i$$

where β_0 is the intercept, β_1 is the coefficient associated with time of evaluation, β_2 is the coefficient associated to treatment allocation and β_3 is the coefficient associated with the interaction between time and treatment allocation. We are interested in the estimation of β_3 because is the parameter that quantifies if the GHS score evolution is different between treatment arms. On the other hand, β_2 is only associated with treatment differences at baseline where we do not expect to observe any difference.

Table 5 : Results from the liner model

	Estimate	95% CI	T value	P-value
Intercept	-2.88	(-6.27; 0.51)	-1.66	0.097
$\hat{\beta}_1$ (Time)	-21.36	(-27.18; -15.54)	-7.20	**<0.001**
$\hat{\beta}_2$ (Treat)	1.22	(-3.78; 6.22)	0.48	0.63
$\hat{\beta}_3$ (Treat*time)	17.29	(8.55; 26.03)	3.88	**<0.001**

The linear model shows that β_1 is statistically different to 0, showing a decrease in the GHS score over time in the reference treatment (CT treatment). There are not differences in baseline scores regarding treatment allocation (β_2). However, the interaction is statistically significant (β_3). The positive value in β_3 shows a better evolution in the GHS score with the L+R treatment over the time compared to the CT treatment.

On one hand, the model estimates that at the end of the treatment (time=1, pre-surgery time-point) in average the GHS score will decrease 21.36 points from baseline in patients receiving CT. On the other hand, in patients receiving L+R treatment the average GHS score only will decrease 4.07 points from baseline (-21.36 + 17.29= -4.07). The estimate between-group difference in change from baseline is 17.29 (95%CI 8.57 - 26; p-value < 0.001) showing a better GHS evaluation with L+R treatment. Or in other words, in both treatments patients suffered a decreased of GHS values, but the decrement is less remarkable in patients receiving the L+R treatment.

Results in the Tobit model

In the Tobit model, we define that the potential range of change from baseline values was [-100, 100]. The results are very similar to the estimation obtained in the linear model. The fact that the observed values are far from the interval ranges (the majority of values are within the [-20,20] interval), makes no difference in the model estimation compared with the linear model. The same conclusions using the linear model results could be extrapolated to the Tobit model estimation.

Table 6 : Results from Tobit model

	Estimate	95% CI	T value	P-value
Intercept	-2.88	(-6.25; 0.49)	-1.67	0.096
$\hat{\beta}_1$ (Time)	-21.36	(-27.18; -15.54)	-7.20	**<0.001**
$\hat{\beta}_2$ (Treat)	1.22	(-3.78; 6.22)	0.48	0.63
$\hat{\beta}_3$ (Treat*time)	17.29	(8.55; 26.03)	3.88	**<0.001**

Results for the linear mixed model

When modelling the scores by means of the linear model (or Tobit regression) they are assumed independent. However, it has to be taken into account that the same individual reported several scores at different time-points (repeated measurement). The linear mixed model, by means of random effects, takes care of the repeated measurement structure. In particular, we have included random effects in the intercept and in the slope, as well as a correlation between random effects (model option 5 in section 3.3). The estimated results for the fixed effects are reported in the above table:

Table 7 : Results from the linear mixed model

	Estimate	95% CI	T value	P-value
Intercept	-2.50	(-5.52; 0.52)	-1.63	0.11
$\hat{\beta}_1$ (Time)	-23.25	(-29.09; -17.41)	-7.80	**<0.001**
$\hat{\beta}_2$ (Treat)	1.20	(-3.17; 5.57)	0.454	0.59
$\hat{\beta}_3$ (Treat*time)	17.77	(9.26; 26.28)	4.10	**<0.001**

Again, as observed in the linear model and in the Tobit model, the parameter β_3 is statistically significant showing a worse evolution in GHS scores over the time in patients receiving CT treatment.

The model including the random effects, and using the R function *lmer*, is as follows:

```
> lmer( global_change ~  dif2*Arm+ (dif2| ID.patient), data =tfm)
Linear mixed model fit by REML ['lmerModLmerTest']
Formula: global_change ~ dif2 * Arm + (dif2 | ID.patient)
   Data: tfm
REML criterion at convergence: 5936.326
Random effects:
Groups      Name        Std.Dev. Corr
ID.patient (Intercept)  7.146
           dif2        15.044   0.79
Residual               12.980
```

where

$$Change\ GHS_i = (\beta_0 + \boldsymbol{b_{i0}}) + (\beta_1 + \boldsymbol{b_{i1}}) * time_i + \beta_2 * Treat_i + \beta_3 * Treat_i * time_i + \varepsilon_i$$

if we substitute the parameters by the model estimation, then:

$$Change\ GHS_i = (-2.5 + \boldsymbol{b_{i0}}) + (-23.25 + \boldsymbol{b_{i1}}) * time_i + 1.2 * Treat_i + 17.77 * Treat_i * time_i + \varepsilon_i$$

$$b_i \sim N_2(0, D), \qquad \varepsilon_i \sim N_{ni}(0, 12.98^2 I_{ni})$$

$$D = \begin{pmatrix} 7.146 & 0 \\ 0 & 15.044 \end{pmatrix} \begin{pmatrix} 1 & 0.79 \\ 0.79 & 1 \end{pmatrix} \begin{pmatrix} 7.146 & 0 \\ 0 & 15.044 \end{pmatrix}$$

and b_{i0} and b_{i1} are the random effects for the intercept and the slope, respectively. Note that here, 7.146 is the standard deviation estimation for random effects at intercept and 15.044 the standard deviation for random effects at slope. The 12.98 is the standard deviation for the residuals. Finally, the 0.79 is the estimation of the correlation between random effects (intercept and slope). The positive correlation shows that individuals with high higher values in the intercept has a more positive slope. In other words, individuals with better HRQoL outcomes at baseline had a better evolution over the time.

5.4.2 Analysis of the absolute score

At that point, all used statistical methods were focused on the study of changes from baseline (normally distributed values). However, it could be our interest to study the absolute score values, especially, the original row values without the scaling transformation. In that case, the response variable is usually an ordinal outcome not normally distributed. The original GHS values range from 0 (poor GHS outcomes) to 14 (very good outcomes).

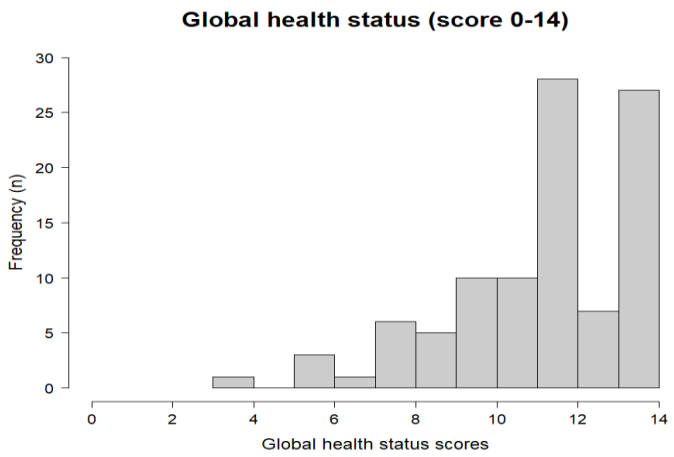


Figure 10: Histogram of *global health status* score at baseline in the original scale (from 0 to 14) in patients included in the Coralleen trial

In this situation, we cannot use the previously reported methods (liner model, linear mixed models and Tobit regression) because the response variable is not normally distributed. Here we will explore i) generalised linear mixed model using the logistic function and ii) the beta-binomial mixed model where both models assume the existence of a sum of 14 Bernoulli-dependent variables (since the maximum score is 14) whose probability parameter is (p_i), and both models estimate p_i (see section 3.3 and 3.4 for more details).

Generalised linear mixed (logistic function)

To estimate the generalized linear model we will use the R function *glmer* (the R function *Blmm* from the package *PROreg* it can also be used but the computation time is larger). The implementation in R of this model is not straightforward, so we describe some details to better understand the practical application. In the R *glmner* function, we define *family=binomial* to use the logistic link. The response variable is a matrix with two columns, i) the first column is the score of each patient in each evaluation, ii) second column is the maximum score (now 14) minus the score of each patient in each evaluation:

```
cbind(tfm$global_ordinal,max-tfm$global_ordinal)
     [,1] [,2]
[1,]   14    0
[2,]   12    2
[3,]   12    2
[4,]   12    2
[5,]   14    0
```

The first patient in the first evaluation has a score of 14, in the second evaluation of 12, etc. Then, we use the same model for the response than in the linear mixed model (random effects in the intercept and in the slope will be included, as well as a correlation between random effects). Table 8 reports the results of this model:

Table 8 : Results from the generalized linear mixed model

	Estimate	95% CI	T value	P-value
Intercept	1.48	(1.21; 1.75)	10.86	**<0.001**
$\hat{\beta}_1$ (Time)	-1.079	(-1.35; -0.80)	-7.63	**<0.001**
$\hat{\beta}_2$ (Treat)	0.26	(-0.13; 0.65)	1.29	0.20
$\hat{\beta}_3$ (Treat*time)	0.70	(0.27; 1.13)	3.26	**0.001**

time=1 indicates the end of treatment and treatment=1 is L+R treatment

The model only estimates the fixed effects (β). The most relevant interpretation is the β_3 parameter, that it is the log odds-ratio of the interaction term. Concerning the interpretation β_3 =0.7 implies $\exp(0.70) = 2.01$, and hence receiving the L+T treatment increases by 2.01 the odds of having a higher GHS score in comparison with CT treatment at the end of the study. Since the parameter estimation is statistically different to 0, we can conclude that the odds for better GSH score are higher in patients receiving L+R over the time. In other words, patients receiving the L+R treatment have a higher odds of responding positively to each of the 14 Bernoulli questions showing a better quality of life.

Beta-binomial mixed model

The beta-binomial distribution offers a more flexible approach with the inclusion of a dispersion parameter than could better adjust the response variable in the modeling estimation. Now, we are going to estimate the i) probability parameter of the binomial distribution for the GHS score in the 0-14 scale and ii) probability parameter of the beta-binomial distribution plus the dispersion parameter of the beta-binomial distribution (subsection 3.3 and 3.4).

Table 9 : Parameter estimation using the binomial and the beta-binomial distribution

	Probability parameter	Dispersion parameter
Binomial distribution	0.745	-
Beta-binomial distribution	0.745	0.127

To visualise those results, we will plot the histogram with all GHS scores in the 0-14 scale and we will overlap the density distribution of the binomial and beta-binomial distribution.

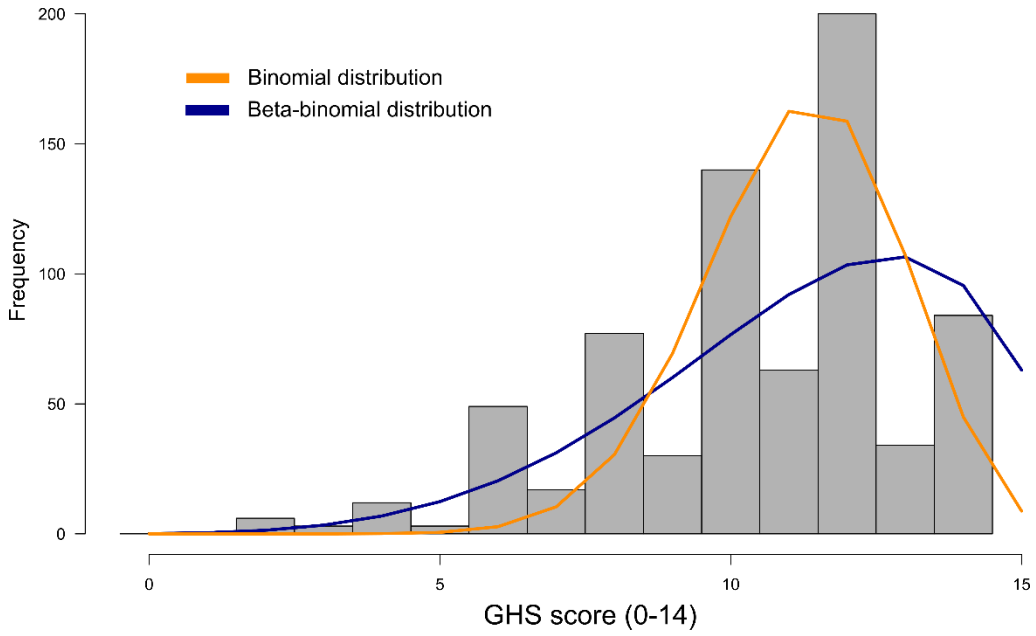


Figure 11: Histogram of *global health status* score in the original scale (from 0 to 14) and density function estimation using the binomial and beta-binomial distribution.

Then, we will use the R function *BBmm* to estimate the beta-binomial mixed-effects model, including a random intercept and random slope to adjust for repeated measurement data.

Table 10 : Results from the beta-binomial mixed model

	Estimate	95% CI	T value	P-value
Intercept	1.43	(1.31; 1.55)	22.72	**<0.001**
$\hat{\beta}_1$ (Time)	-1.01	(-1.21; -0.81)	-9.85	**<0.001**
$\hat{\beta}_2$ (Treat)	0.23	(0.03; 0.43)	2.38	**0.02**
$\hat{\beta}_3$ (Treat*time)	0.70	(0.37; 1.03)	4.23	**<0.001**

In this case, the estimation is very similar to the one observed with the logistic mixed model. The β fixed regression coefficients are equivalent to the log odds-ratio in a binomial logistic regression model[22]. If we focus in β_3 $(\exp(0.70) = 2.01)$, the interpretation is that receiving the L+T treatment increases by 2.01 the odds of having a higher GHS score in comparison with CT treatment at the end of the study.

We can visualise those findings to facilitate results interpretation. First, we can plot the population-average estimation per treatment arm according to i) the beta coefficient and ii) time. As observed, the population-average estimation in the L+R group presents an almost constant slope showing a small modification in quality of life results in those patients over the time. On the other side, the population-average estimation in the CT group presents a negative slope estimation, showing a deterioration in the quality of those patients over the time.

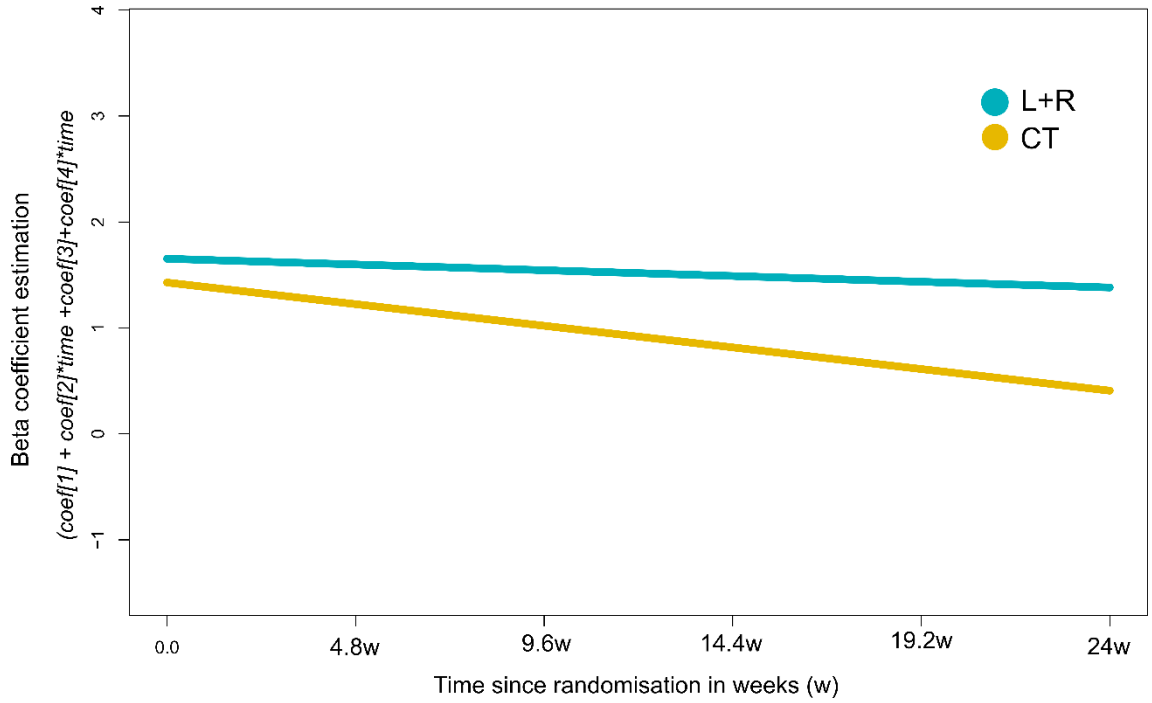


Figure 12: Population-average estimation per treatment arm

Moreover, the model allows to estimate a specific intercept and a specific slope for each individual. In the next figure, we plot the population-average estimation per treatment arm plus the specific estimation for each individual. Overall, patients receiving CT treatment had lower score punctuations during the study follow-up. Consequently, patients receiving CT had a clear deterioration over the time (negative slope) compared with patients receiving L+R treatment.

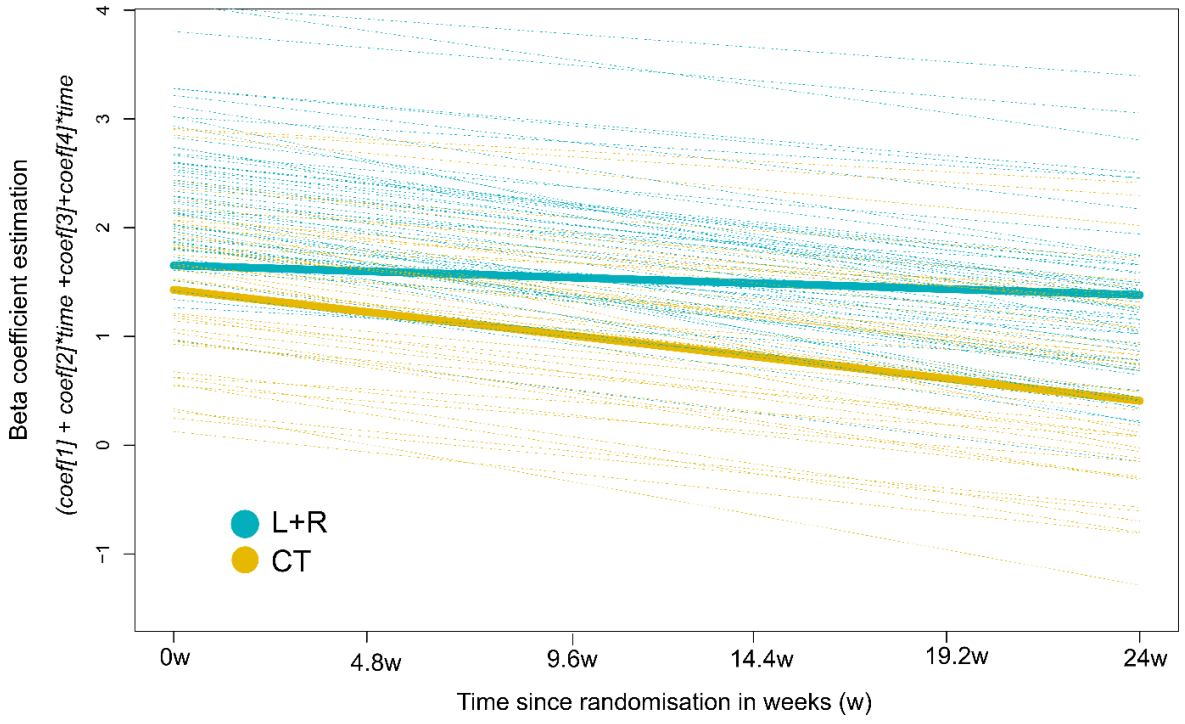


Figure 13: Population-average estimation per treatment arm and specific estimation for each individual using random effects at intercept and slope

5.4.3 Time to health-deterioration

So far, we have analysed *the global health status* (GHS) score 1) using the change from baseline values and 2) using the absolute score (from 0 to 14). However, as defined in section 3.5, another alternative to study health-related quality of life (HRQoL) data is to use a time-to-event approach. In this situation, we have to start with an unambiguous definition of the event of *health-deterioration*. We start defining the event of health deterioration as that first time where there is *at least 10-points diminution* of the HRQoL score compared with the baseline measurement. In this situation the Kaplan-Meier curves can be reported for illustration purposes.

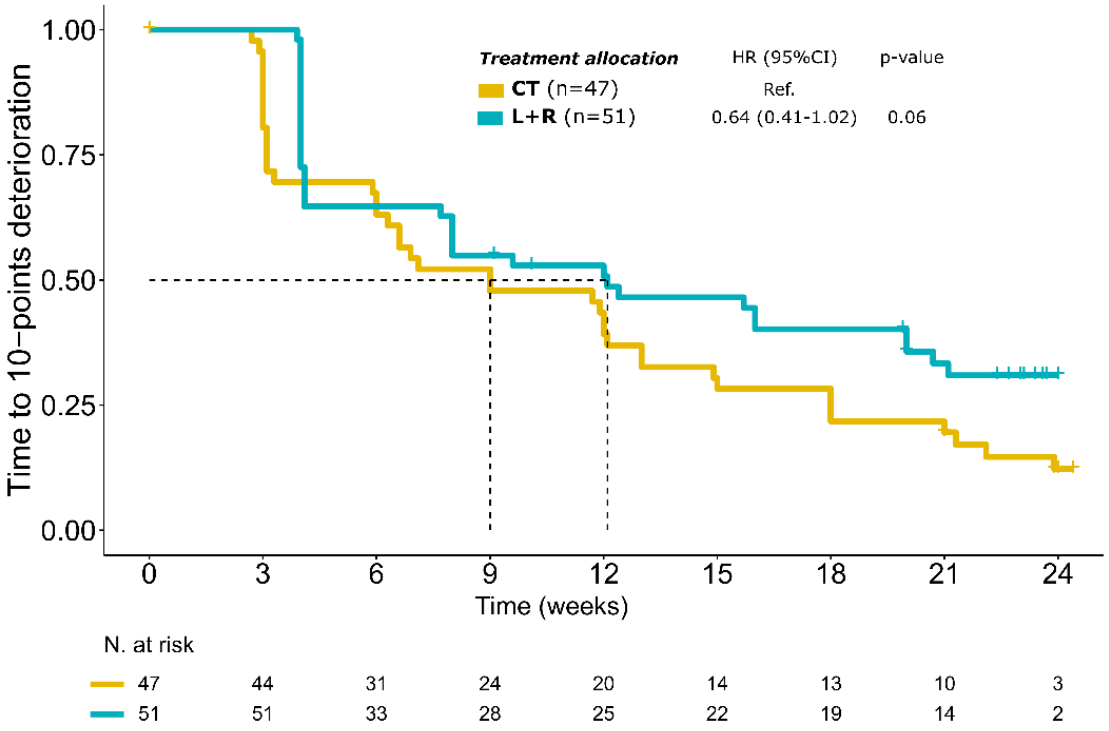


Figure 14: Kaplan-Meier curves to estimate time to health-deterioration (defined as 10-points deterioration) per treatment

Visually speaking, the risk of *health-deterioration* event was similar during the first 6 weeks in both treatment arms, but after month sixth the CT group showed a higher risk of health deterioration (Figure 14). In case of a violation of the proportional hazard assumptions, the standard Cox model cannot be used. However, we formally tested if there is enough evidence to reject the null hypothesis of proportional hazards (*cox.zph* function in R). With a p-value of 0.9, we do not have enough evidence to prove the violation of the proportional assumptions and we calculate the Cox model. The result shows a hazard ratio (HR) = 0.64 (95% 0.41-1.02), p-value of 0.06.

Next, we re-define the event of health deterioration as *at least 40-points* diminution of the HRQoL score compared with the baseline measurement. In this case, less events are reported, but a clear benefit in favour of the L+R treatment is observed. The hazard ratio of 0.22 indicates that the risk of health deterioration is reduced in a 78% with L+R treatment compared to CT treatment. In fact, very few patients from L+R group suffered health deterioration using this event definition (Figure 15).

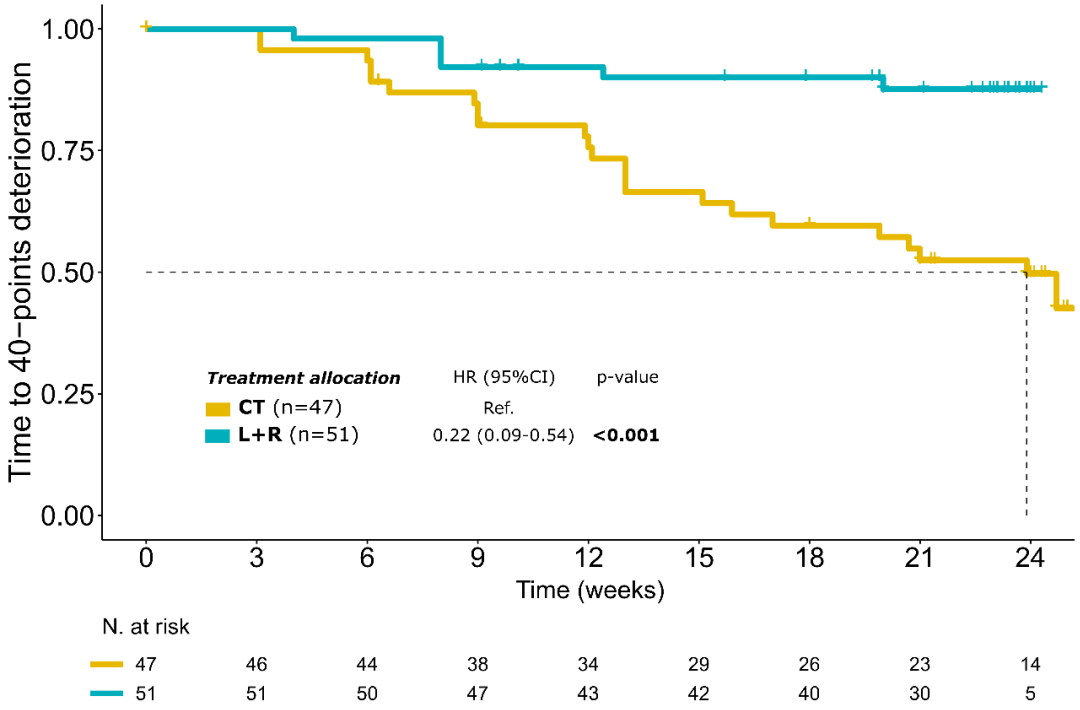


Figure 15: Kaplan-Meier curves to estimate time to health-deterioration (defined as 40-points deterioration) per treatment

We tried to validate the model by means of Schoenfeld residuals. The small number of events did not allow us to clearly validate the model (ideally, we would like to observe a horizontal line estimation).

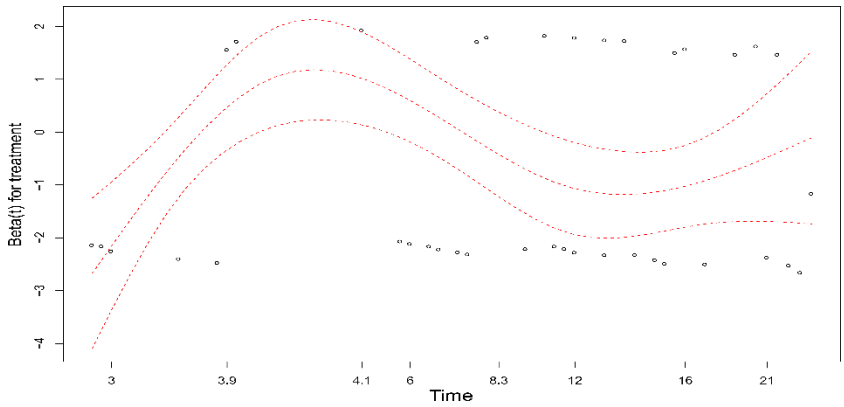


Figure 16: Scaled Schoenfeld residuals, along with a smooth curve

More importantly, the PROs outcomes were not collected at the same time point in both treatment arms (every 3 weeks in patients receiving CT and every 4 weeks in patients receiving L+R treatment). For that reason, the use of time-to-event analysis to analyse quality of life data in the Coralleen trial is biased and should not be used. The hazard ratio is an unbiased estimation if the time between evaluations is the same in both groups. However, the estimation will be biased if the timing is different between treatment arms. In the case of the Coralleen trial, even in a scenario of similar quality of life outcomes, the median time to health-deterioration will be shorter in the CT group because evaluations in this group are performed in a shorter time period.

5.4.4 Missing data

All reported results have been calculated in patients with the available information without data imputation, which for the Coralleen trial corresponds to more than 90% of patients reporting HRQoL data and more than 73% of patients completed all the study questionnaires over the duration of the receiving treatment (see first part of section 5.2). However, as explained in section 3.7, missing data is a common problem in HRQoL analysis and it is an important issue to be addressed.

In this section, we will study how different strategies to deal with missing data could impact in results estimation. Trying to simplify all possible combinations and trying to help results interpretation, we will focus on the specific case of the change from baseline analysis using the linear mixed model (section 5.4.1, linear mixed model). The estimation of the β_3 parameter will be reported under different missing data strategies.

Table 11: Results estimation under different techniques to deal with missing data

Method	β_3 (95% CI) estimation
No data imputation	17.77 (9.26; 26.28)
Only patients with all evaluations are included	19.34 (10.19; 28.48)
Imputation using the mean score per treatment arm in each evaluation	6.87 (0.75; 13.00)
Imputation using the last observed value of the same patient	12.69 (4.03; 21.34)
Imputation using the worst-case scenario (40-points deterioration from baseline)	11.65 (3.43; 19.88)

In all scenarios, the β_3 parameter is statistically different to 0, showing a better evolution in the GHS score with the L+R treatment over the time compared to the CT treatment.

The largest differences are obtained in the scenarios of *no data imputation* and *using only patients will all evaluations*. In both scenarios, no imputation is performed. The *no data imputation* scenario uses all available information while the *only patients with all evaluations* excluded patients who reported some but not all questionnaires. In this second scenario the sample size is smaller and, consequently, the confidence interval estimation is wider.

The other three methods use imputation for missing data. The magnitude of the difference between-groups is smaller compared with the first two methods. The third method imputes the missing value with the mean score of that evaluation in patients receiving the same treatment. This method can be used if we assume that the missing data is completely at random at only depends on the patient's covariate (in this case, treatment arm). The fourth scenario imputes the missing value with the last observed value of the same patient. However, we have observed that in Coralleen trial it exists a general trend of deterioration of quality of life over the time. For that reason, this approach could not be the most appropriated in our case. The last scenario imputes the missing value with a – 40

score. This method can be applied when we assume that the missing data is not at random and we want to test the robustness of the results using worst-case scenario for missing values. Overall, using imputation the sample size is larger and the confidence interval estimation is narrower.

5.5 HRQoL analysis of other scales

Section 5.4 has been fully dedicated to analyse the *global health status* (GHS) score of the EORTC QLQ-C30 questionnaire from a longitudinal perspective. Nevertheless, the quality of life data in Coralleen trial is not restricted to the GHS score. As described in sections 4.2 and 5.2, the trial also collected information of 9 functioning scales and 13 sysmptoms scales. Same methodology presented in section 5.4 can be used to study the other scales. We will not replicate all the analysis for the other scales because that will make the work extremely extensive and because it does not represent any novelty from a statistical perspective.

We will restrict our attention to the evolution of the change from baseline values in some scales and we will discuss certain peculiarities that can be interesting from a statistical point of view. In the next serie of plots, we can observe the evolution of the change over the time from baseline values in four specific functioning scales (Figure 17 - 20). The higher the functioning scale, the better the HRQoL condition. Figures related to all functioning scales can be found in Appendix 1.

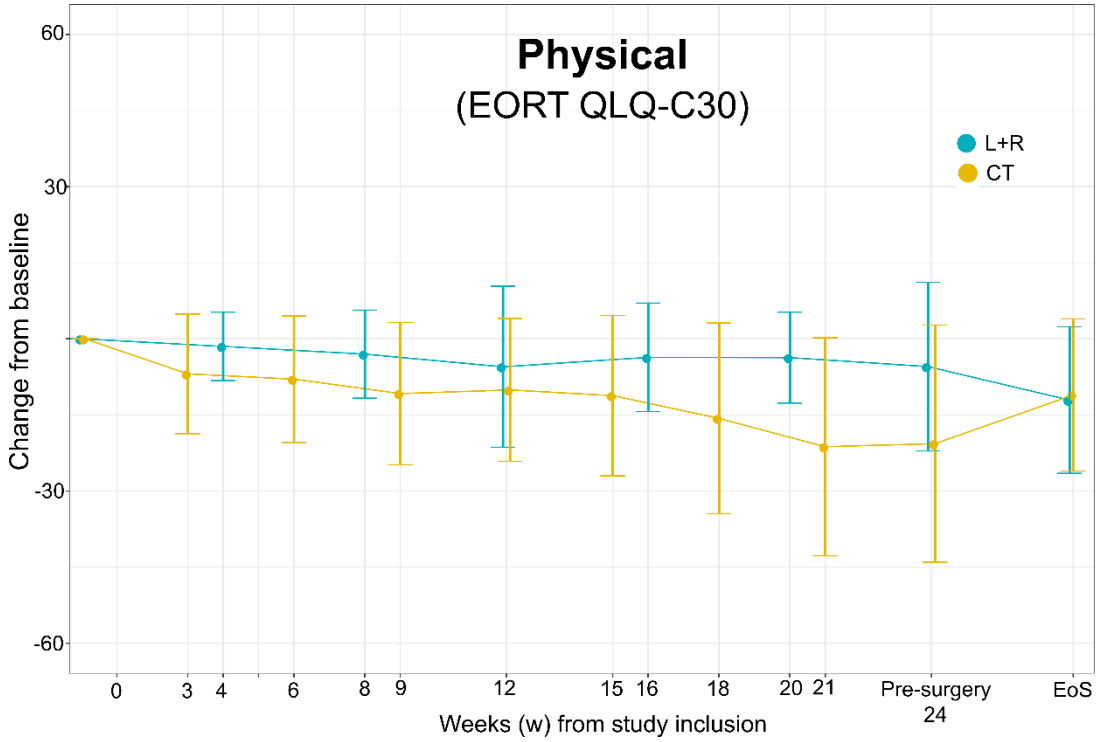


Figure 17: Evolution of the mean change from baseline values in the physical functioning scale (along with the mean ± standard deviation) according treatment arm

Overall, the L+R group presented a better *physical* functioning than patients treated with CT (Figure 17). The mean change from baseline score progressively decreased in the CL group, but it is almost constant in the L+R group. After the end of the treatment (EoS time-point) the values are again similar in both treatment arms.

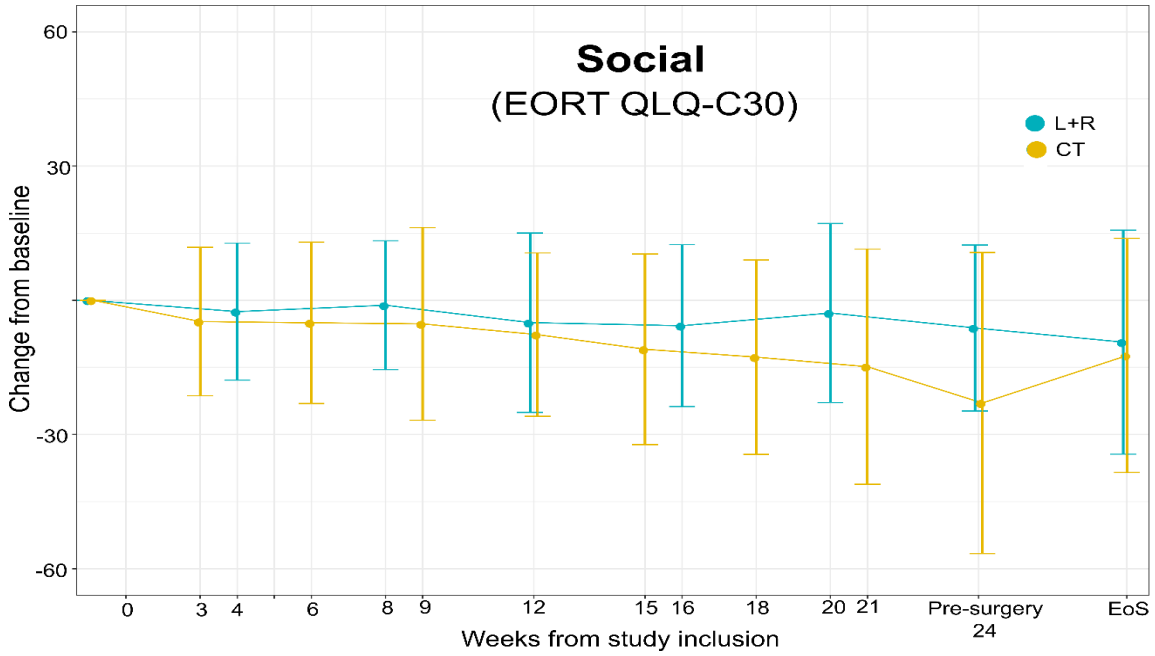


Figure 18: Evolution of the mean change from baseline values in the social functioning scale (along with the mean ± standard deviation) according treatment arm

The *social* functioning scale presents similar results that the physicologial scale. The mean change from baseline score progressively decreased in the CL group. It also decreases in the L+R group but with lower intensity. The time-point with a higher between-group difference is *pre-surgery*.

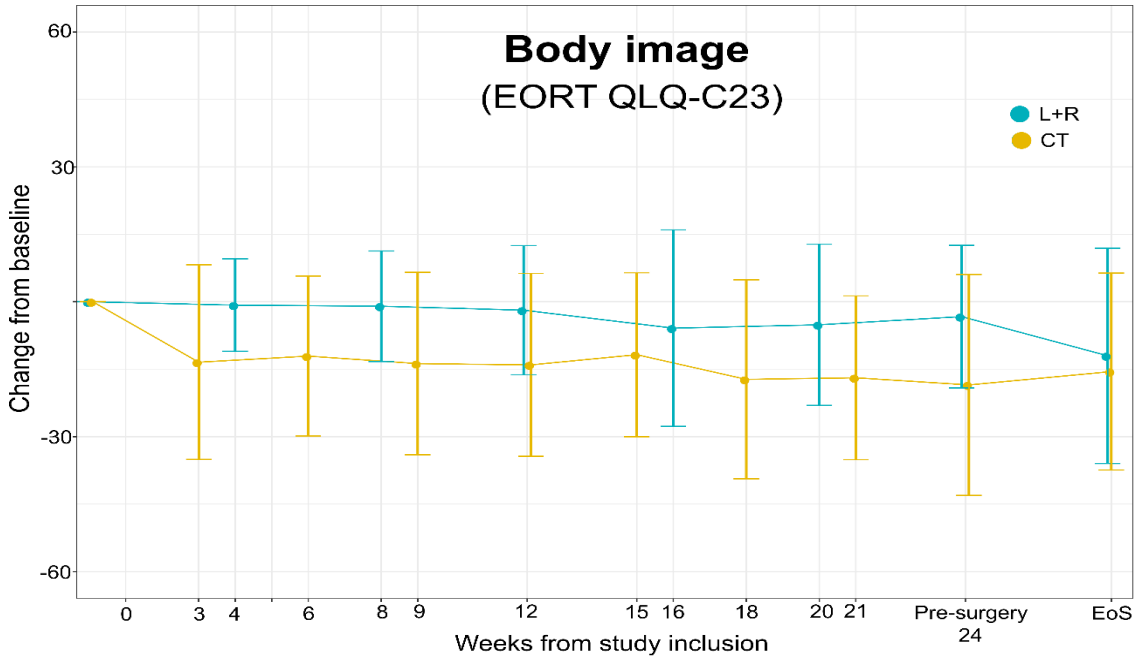


Figure 19: Evolution of the mean change from baseline values in the body image functioning scale (along with the mean ± standard deviation) according treatment arm

In terms of *body image* (Figure 19), the mean change from baseline decrease dramatically in patients receiving CT during the first three weeks. After that point, the mean change remains constant but with lower levels compared with patients in the L+R group.

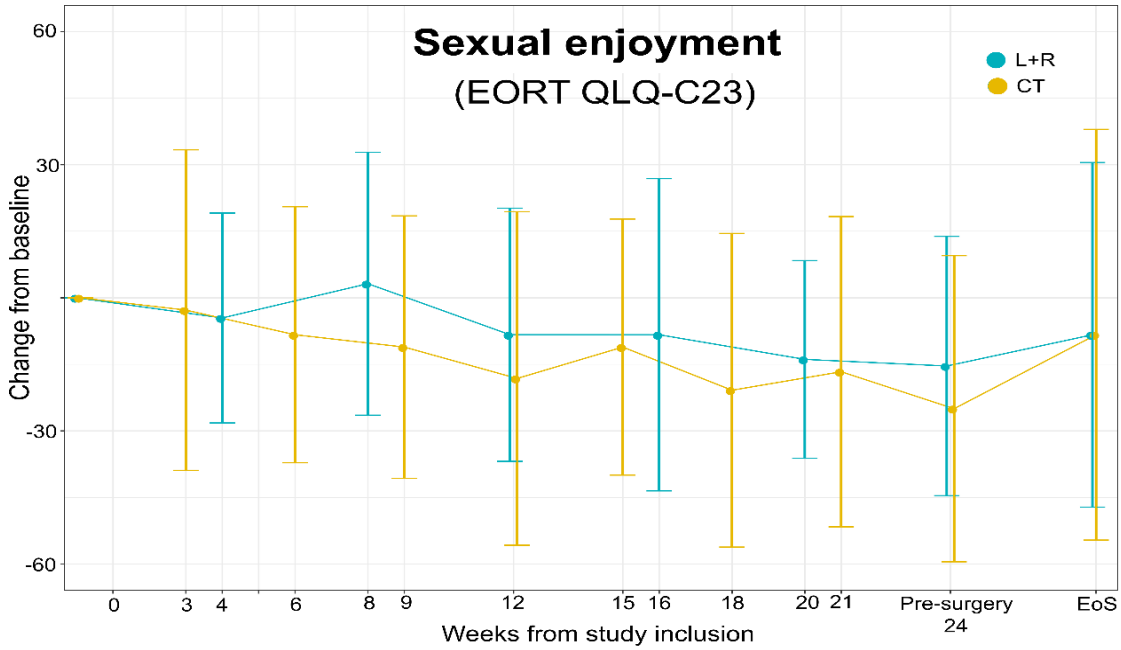


Figure 20: Evolution of the mean change from baseline values in the sexual enjoyment functioning scale (along with the mean $\pm$ standard deviation) according treatment arm

In Figure 20, we observe the evolution of the *sexual enjoyment* functioning scale. In comparison with the other scales, here we observe a wider estimation of the standard deviation in each time-point. The reason for that, is the low compliance rate on this scale (less than 50% at baseline, see section 5.2). As the sample size is lower, the estimation has more variability.

In Table 12, we report the estimated mean change from baseline to pre-surgery in all the functioning scales. In this table, we estimate the expected change from baseline in CT patients at pre-surgery (β_1 estimation), the expected change from baseline in L+R patients at pre-surgery (β_1 - β_3 estimation) and the difference in the mean change between groups (β_3 estimation) using the linear mixed model. In the *physical scale*, at pre-surgery , it is expected an average decrease of 4.3 points from the baseline score in patients receiving L+R. The average decrease is 20.3 points in patieng receiving CT, with a mean treatment difference of 16 points.

Table 12: Changes from baseline estimated in all functioning scales using a repeated-measures linear mixed-effect model

	Estimated mean change from baseline to pre-surgery (95% CI)		Difference in the mean change in L+R vs. CT (95% CI)
	L+R	CT	
Functional scales			
• Physical[1]	-4.3 (-9.5; 0.8)	-20.3 (-25.5; -15.1)	16 (8.7; 23.2)
• Social[1]	-6.3 (-13; 0.4)	-19.7 (-26.1; -13.4)	13.4 (4.2; 22.6)
• Emotional[1]	-0.7 (-7.4; 6.0)	-6.8 (-13.3; -0.2)	6.1 (-3.3; 15.4)
• Role[1]	-4.8 (-11.8; 2.2)	-26.7 (-33.7; -19.7)	21.9 (12; 31.8)
• Body imagine[2]	-3.2 (-8.9; 2.5)	-12.9 (-18.5; -7.3)	9.7 (1.7; 17.7)
• Sexual enjoyment[2]	-5.3 (-20.4; 9.9)	-36.1 (-54.4; -17.8)	30.8 (7.2; 54.5)

[1]EORTC QLQ-C30, [2]EORTC QLQ-BR23 questionnaires. CI, confidence interval

All figures regarding the evolution of symptom scales over the time can be found in Appendix 2. Here, we will present the plots for two specific symptom scales *appetite loss* and *pain* (Figure 21-22). In symptom scales, the lower the score, the better the HRQoL condition.

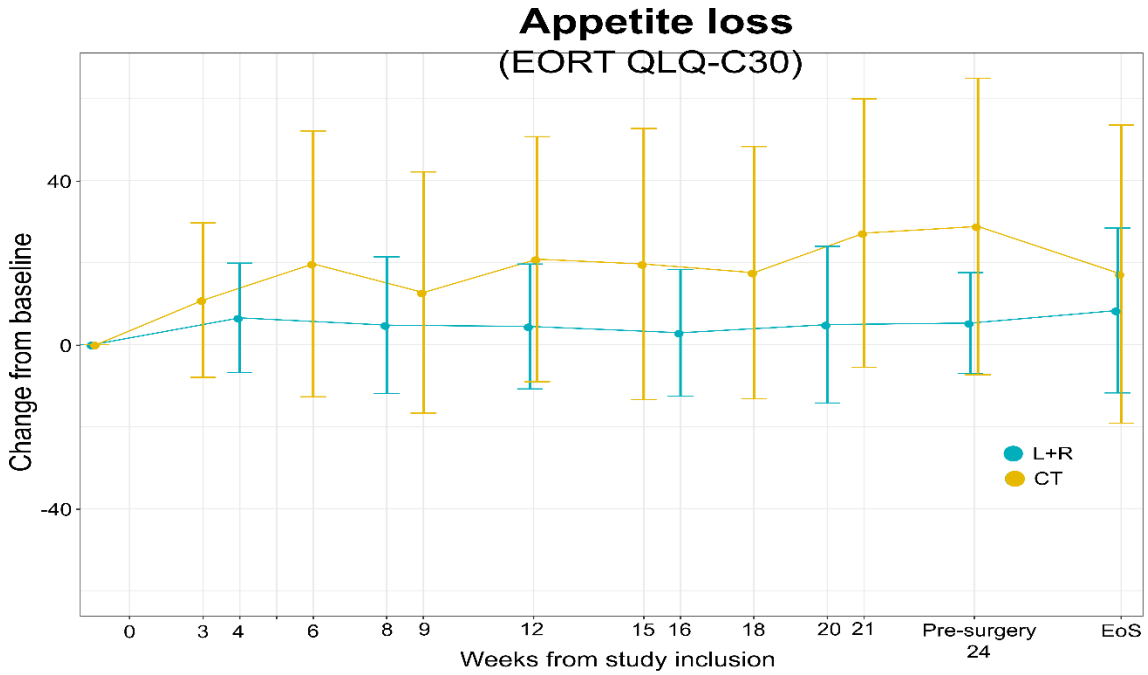


Figure 21: Evolution of the mean change from baseline values in appetite loss symptom scales (along with the mean ± standard deviation) according treatment arm

In the *appetite loss* scale (Figure 21), we observe that the score increase in CT patients while it remains almost constant in patients receiving L+R treatment. As higher punctuations are associated with worse HRQoL in symptom scales, patients receiving CT have a worst quality of life in terms of *appetite loss.*

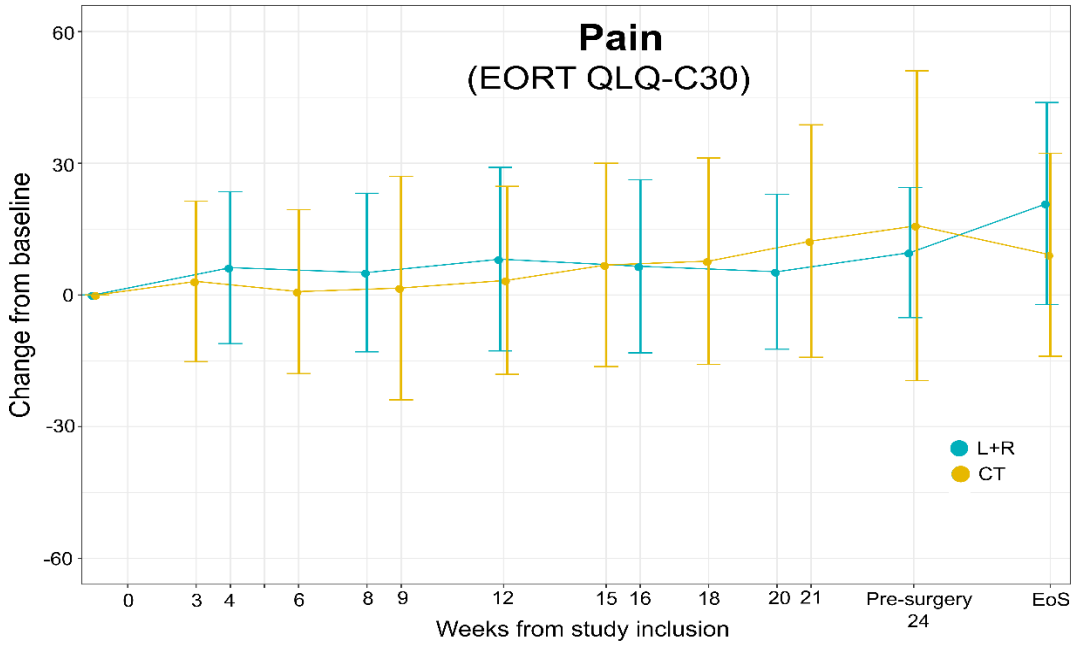


Figure 22: Evolution of the mean change from baseline values in pain symptom scales (along with the mean $\pm$ standard deviation) according treatment arm

No differences were observed in the *pain* scale between patients receiving L+R or CT treatment. The scores increase progressively in both treatment arms (Figure 22).

In Table 13, we estimate the expected change from baseline in CT patients at pre-surgery (β_1 estimation), the expected change from baseline in L+R patients at pre-surgery (β_1 - β_3 estimation) and the difference in the mean change between groups (β_3 estimation) using the linear mixed model.

Table 13: Changes from baseline estimated in all symptom scales using a repeated-measures linear mixed-effect model

	Estimated mean change from baseline to pre-surgery (95% CI)		Difference in the mean change in L+R vs. CT (95% CI)
	L+R	CT	
Functional scales			
• Fatigue[1]	5.9 (-1.0; 12.8)	34.6 (27.8; 41.5)	28.7 (19; 38.5)
• Financial difficulties[1]	6.0 (-0.8; 12.9)	13.8 (7.3; 20.4)	7.8 (-1.6; 17.2)
• Diarrhoea[1]	-0.8 (-8.7; 7.1)	12.6 (4.7; 20.4)	13.4 (2.6; 24.6)
• Constipation[1]	7.9 (1.3; 14.5)	4.7 (-1.6; 11)	-3.2 (-12.3; 5.9)
• Appetite loss[1]	3.2 (-5.2; 11.6)	26.1 (17.7; 34.4)	22.9 (11; 34.8)
• Insomnia[1]	4.5 (-3.3; 12.2)	10.7 (3.2; 18.1)	6.2 (-4.6; 16.9)
• Dyspnoea[1]	3.3 (-3.6; 10.2)	13.6 (6.8; 20.4)	10.3 (0.5; 20.0)
• Pain[1]	4.6 (-2.1; 11.4)	16.1 (9.5; 22.7)	11.5 (2.0; 20.9)
• Nausea and vomiting[1]	0.6 (-3.2; 4.3)	-1.9 (-5.4; 1.7)	-2.5 (-7.6; 2.7)
• Systematic therapy side effects[2]	9.4 (4.4; 14.4)	20.7 (15.8; 25.5)	11.3 (4.3; 18.2)
• Upset by hair loss[2]	14.5 (-5.9; 34.8)	24.9 (4.9; 44.9)	10.4 (-18.1; 39.0)
• Arm symptoms[2]	0.6 (-4; 5.3)	2.6 (-2.1; 7.2)	2 (-4.6; 8.5)
• Breast symptoms[2]	-2.4 (-6.2; 1.4)	0 (-3.7; 3.7)	2.4 (-2.9; 7.7)

[1]EORTC QLQ-C30, [2]EORTC QLQ-BR23 questionnaires. CI, confidence interval

In conclusion, L+R is associated with better quality of life outcomes over the time in *fatigue, diarrhoea, appetite loss, dyspnoea, pain* and *systematic therapy side effects*. On the other symptom scales, no statistically significant differences are observed between L+R and CT treatment.

The same analysis on functioning and symptom scales could be performed with the original score using the generalized linear mixed model (logistic link) or the beta-binomial mixed model. But, as mentioned previously, we will not present those results to avoid an extremely extensive work. Nevertheless, we will present a concrete example to better understand the difference between the binomial and the beta-binomial distribution.

In section 5.3 we have presented the fitting of the binomial and the beta-binomial distribution in the *global health status* (GHS) score (Figure 11). Additionally, we observed that no differences were found in the model estimations (Table 8 and 10). In that situation, following the principle of parsimony, the use of the binomial distribution is recommended. However, in situations where the score distribution is very skewed, the beta-binomial distribution could provide a better adjustment. We can use the example of the *physical functioning* score (extreme left skewed), where the flexibility that provides the beta-binomial distribution could facilitate a better adjustment (Figure 23).

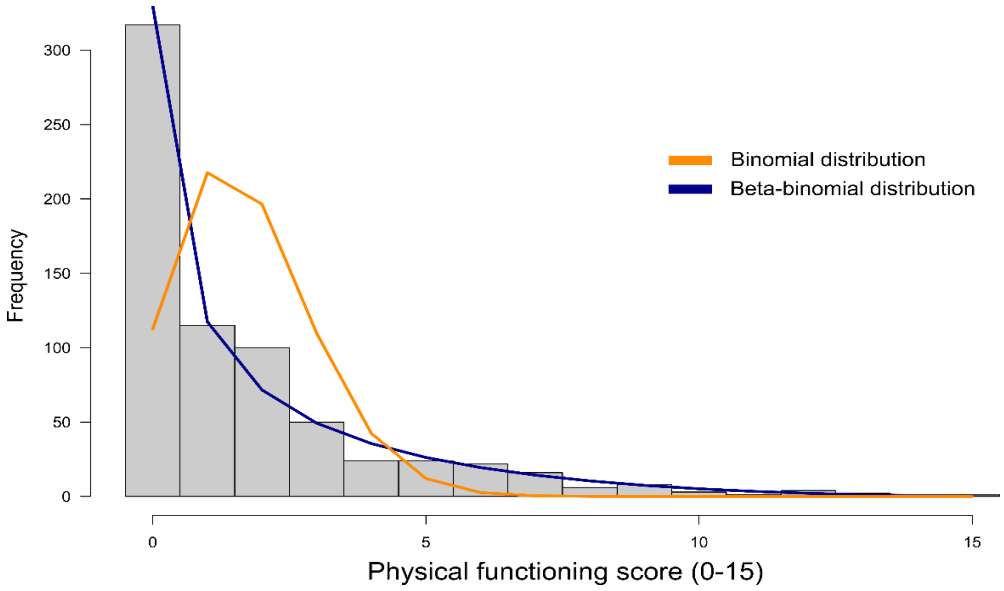


Figure 23: Histogram of *physical functioning* score in the original scale (from 0 to 15) and density function estimation using the binomial and beta-binomial distribution.

Consequently, some difference can be found in the point estimation of the fixed parameter coefficients when using the binomial distribution or the beta-binomial (Table 14 and 15).

Table 14 : Results from the generalized linear mixed model to model the physical *functioning score*

	Estimate	95% CI	T value	P-value
Intercept	-3.33	(-3.88; -2.78)	-11.84	**<0.001**
$\hat{\beta}_1$ (Time)	2.03	(1.56; 2.50)	8.37	**<0.001**
$\hat{\beta}_2$ (Treat)	-0.70	(-1.48; 0.08)	-1.72	0.09
$\hat{\beta}_3$ (Treat*time)	-1.04	(-1.75; -0.33)	-2.87	**0.004**

Table 15 : Results from the beta-binomial mixed model to model the physical *functioning score*

	Estimate	95% CI	T value	P-value
Intercept	-3.01	(-3.21; -2.81)	-29.88	**<0.001**
$\hat{\beta}_1$ (Time)	1.75	(1.44; 2.06)	11.30	**<0.001**
$\hat{\beta}_2$ (Treat)	-0.56	(-0.91; -0.21)	-3.17	0.01
$\hat{\beta}_3$ (Treat*time)	-1.01	(-1.56; -0.46)	-3.54	**<0.001**

5.6 Pre-surgery evaluation

In section 5.2 we have studied the baseline HRQoL outcomes and we have observed that no differences were presented at baseline between treatment arms. In this section, we will focus on quality of life scores at pre-surgery evaluation (last moment where patients received the treatment).

Functioning scales

At the end of treatment, the L+R group presented higher absolute values in all functional scales, especially in terms of *physical, social, role* and *body image* scales (higher values are associated with better HRQoL in functional scales) (Figure 24).

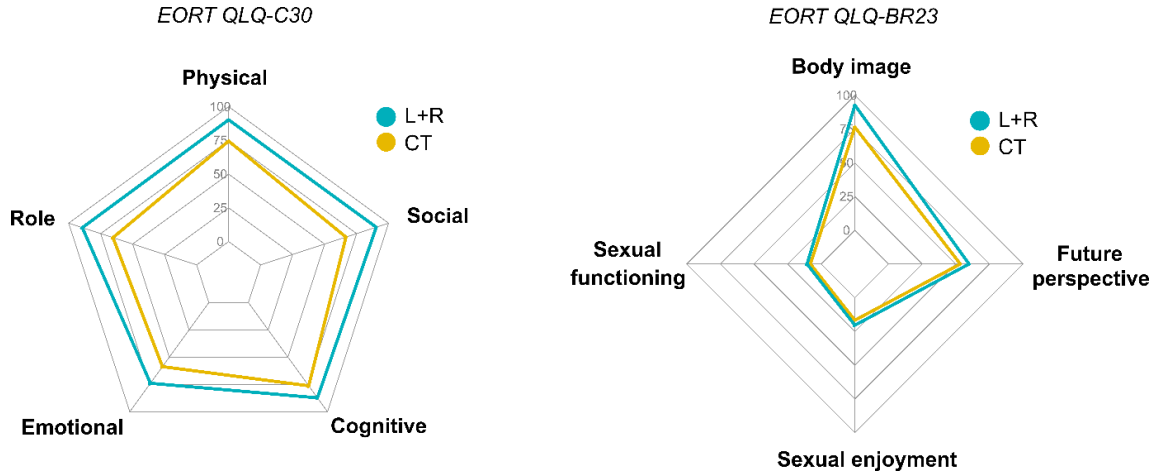


Figure 24: Radar chart with the mean score at pre-surgery in functioning scales per treatment arm

Symptom scales

At the end of treatment, the L+R group presented lower absolute values in all symptom scales, especially in terms of *fatigue, appetite loss* and *upset by hair loss* (lower values are associated with better HRQoL in symptom scales) (Figure 25).

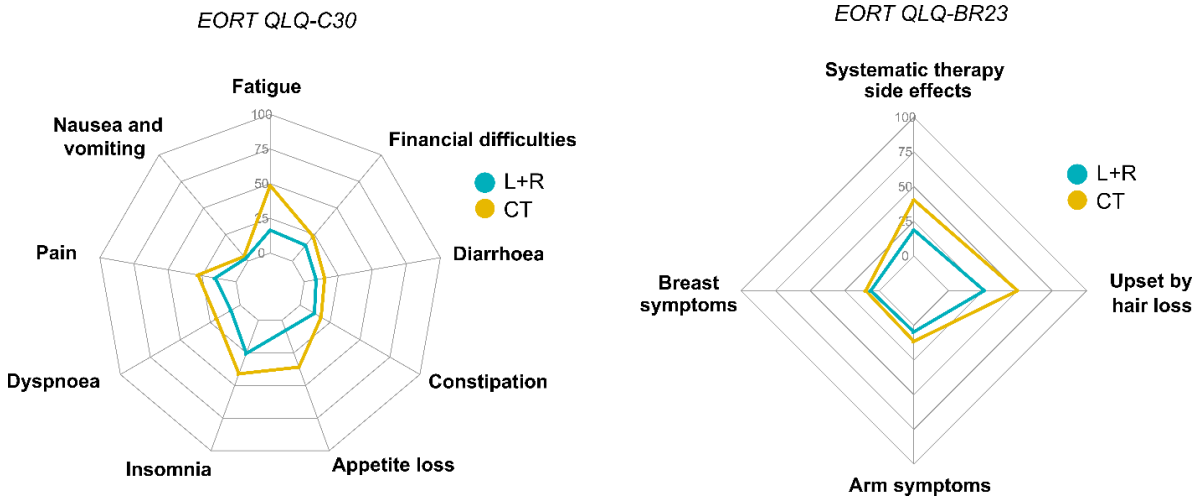


Figure 25: Radar chart with the mean score at pre-surgery in symptom scales per treatment arm

6. Discussion

The statistical analysis of the Coralleen trial has proved to be useful to identify some practical recommendations for those studies involving health-related quality of life (HRQoL) data. The first and more general recommendation is that longitudinal analysis provides a better understanding of quality of life results compared to a specific time-point analysis (cross-sectional approach). The use of longitudinal analysis allows a comprehensive interpretation of the evolution of the quality of life scores of a patient over the time. Furthermore, an analysis for specific time-points only provide a partial view of the outcomes evolution and it has to face with the problem of adjustment for multiple testing.

Moreover, we describe how the right statistical modelling for quality of life data in the context of a randomised clinical trial should use random effects to deal with the repeated measurement structure (mixed models). In our case, we have included random effects in the intercept and slope for the model estimation. This approach allows to estimate a specific intercept and a specific slope for each individual in the trial. However, the inclusion of both random effects (intercept and slope) is not always necessary and it will depend on the study question and on the nature of the study data. In some situations, we could be interested in the inclusion of random effects in the intercept but not in the slope. Consequently, we will obtain a specific intercept per each individual, but a population-average slope estimation per treatment arm. On one hand, we consider that the inclusion of random effects in the slope can provide more flexibility, allowing for a more subject-specific estimation, but the decision of its inclusion is up to researchers involved in the trial. On the other hand, we strongly recommend the use of random effects at intercept. Although in a randomised trials no global differences are expected to be found at baseline between treatment arms, patients included in a trial are not homogenous and different scores are expected to be observed between them. The use of random effects at intercept can help to better deal with this heterogeneity.

Another important question in studies with HRQoL data concerns the strategy that will be used to define the scores. In this project, we have defined the following three strategies i) analysis of *change value from the baseline*, ii) analysis of the *absolute score* and iii) *time to health-deterioration*. In my personal opinion, the analysis of change value from the baseline is the easier and a more intuitive strategy. Using the change from the baseline value in each patient, the inter-patient variability is controlled in an intrinsic manner because "*each patient is his/her own control*". If we opt for this strategy, the linear mixed model is a good option to be used because the *change values* are usually normally distributed.

The second option to study HRQoL is by means of the *absolute score* without scaling transformation. The strength of this approach is that we do not have to use scaling procedures and we can work directly with the original data. In consequence, a better interpretation of the clinical magnitude of the difference can be obtained. The limitation of this approach is that we cannot use the normal distribution and other distribution from the exponential family or with conjugate distributions have to be used. Here, we have presented the generalised linear mixed model using the logistic link and the beta-binomial mixed model as a reasonable alternative for the statistical modelling. The binomial distribution can be accepted unless we deal with very skewed distributed scores. In that case, the

binomial distribution can not fit correctly the shape of skewed data and the beta-binomial distribution provides a better adjustment. Consequently, as a practical recommendation, we would encourage to use the binomial distribution if our data is not extremely skewed and the beta-binomial distribution otherwise. One could argue to use the beta-binomial distribution in all situations. This is a reasonable proposal, that can help in the harmonization of methods used for the analysis. However, the computational time in R software to adjust the beta-binomial is longer and sometimes we can find convergence problems in the parameter estimations.

The third strategy is to use a time-to-event approach to analyse HRQoL data. Time-to-event analysis is common in oncology research and the interpretation of those methods is well known. However, two problems arise when using time-to-event analysis in the context of HRQoL data. First, the definition of the *heath-deterioration event* is arbitrary (*10, 20, 40 points deterioration from baseline*, for example) and little consensus is expected to be found in the event definition across studies. The second limitation is that time-to-event analysis can only be used if the time between evaluations is the same in all treatment arms. Otherwise, this method will provide a biased results in favour of the treatment arm with the longer time between visits. Although the event of *heath-deterioration* could occur at any moment of the patient's follow-up, it can only be observed at the evaluation visit. Hence, the information for a given patient will consist on the time interval [L,R} where R is the first evaluation visit where heath-deterioration has been observed and L is the immediate precedint visit. Therefore the schedule between visits will have an impact on these intervals. This is the case of the Coralleen trial, patients receiving chemotherapy had the evaluation visits every three weeks while patients receiving letrozole plus ribociclib (L+R) every four weeks. In this case, the lengths of the intervals are 3 and 4 weeks, respectively, allowing a more precise estimation of time to heath-deterioration in patients receiving chemotherapy. For instance, if a patient suffers the event of heath-deterioration at the second week, it will be collected at week 3 if the patient receives chemotherapy, while it will collect at week 4 if the patient receives L+R treatment. In this case, and outside the scope of this thesis, interval-censored methods should be used to estimate and make inferences on the survival function for the time to heath-deterioration.

To finish with the discussion, we would like to focus on the analysis of missing data. This a very complex topic and the study of missing data patterns is out of the scope of this project. However, we have studied the robustness of the results under different scenarios. It is recommended to perform a series of sensitivity analysis to evaluate the potential impact of missing data in our study. In our specific case, all scenarios showed a better quality of life outcomes in patients receiving the L+R treatment. This fact gives us more security to conclude that our findings are not being biased for missing data.

7. Conclusions

The current TFM project has been focused on the analysis of health-related quality of life (HRQoL) outcomes in randomised oncology clinical trials. From a theoretical perspective, the main objectives of the project were to 1) to understand the questionnaires to collect HRQoL outcomes, 2) to understand the strengths and limitations of the statistical approaches to evaluate quality of life data and 3) to provide recommendations in the analysis of HRQoL data. From a practical perspective, the project aimed to analyse the patient-reported HRQoL of the phase II Coralleen breast cancer clinical trial.

During the project we have observed that different questionnaires are used in the context of oncology clinical trials to evaluate the impact of a new drug on patients' quality of life. The collected data is i) quite heterogeneous, including questions with a different range of answers and ii) it needs to combine answers from different questions to create scales. Additionally, this data has a repeated measurement structure, where the individual responds to the same questions in different time-points. Altogether, the analysis of HRQoL data is challenging.

The current statistical knowledge faces this challenge with an arsenal of statistical methods to analyse HRQoL outcomes. For the inferential part, the inclusion of random effects can deal with the repeated measurement structure. Additionally, different models such as the linear mixed model or the generalised mixed model using the logistic link can be useful to estimate between-treatment difference depending on the nature of the response variable. The beta-binomial distribution was introduced to offer a more flexible approach that can better fit extremely skewed distributions. Even the time-to-event analysis can be used to explore HRQoL data. However, some lack of knowledge is found in result interpretations with a no clear clinical interpretation of the obtained results.

In relation with the analysis of the Coralleen clinical trial, at baseline more than 90% of patients reporting HRQoL data and more than 73% of patients completed all the study questionnaires over the duration of the trial. At baseline, no differences were found in quality of life outcome between patients that receive letrozole plus ribociblib (L+T) or chemotherapy. However, a better quality of life scores were observed during the treatment period in patients that receive L+R in comparison with patients treated with chemotherapy. The differences were statistically significant in the *global health status*, in all the *functioning scales* and in the majority of *symptom scales*.

Overall, the TFM project shows that i) from a practical perspective, L+R treatment can represent an alternative to chemotherapy with better quality of life outcomes in the study population of patients with breast cancer and ii) the project creates an overall statistical framework for the analysis of quality of life data in the context of future randomised oncology clinical trials. Techniques to transform HRQoL data into meaningful clinical information, interval-censored methods for time to health-deterioration and missing data patterns in trials with low percentage of compliance are some topics to be explored in future research.

8. References

1. Sprangers MAG. Quality-of-life assessment in oncology - Achievements and challenges. *Acta Oncol (Madr)*. 2002;41(3):229-237. doi:10.1080/02841860260088764

2. Srivastava A, van den Berg HM. Standardizing patient outcomes measurement to improve haemophilia care. *Haemophilia*. 2016;22(5):651-653. doi:10.1111/hae.13072

3. O'Shaughnessy J. Extending Survival with Chemotherapy in Metastatic Breast Cancer. *Oncologist*. 2005;10(S3):20-29. doi:10.1634/theoncologist.10-90003-20

4. Stein, K.D; Syrjala, K.L; Andrykowski M. Physical and Psychological Long-Term and Late Effects of Cancer. *Cancers (Basel)*. 2008;112(3):2577–2592. doi:10.1002/cncr.23448.Physical

5. National Cancer Institute. SEER stat fact sheets: female breast cancer. 2019. National Cancer Institute. SEER stat fact sheets: female breast cancer. 2019. Accessed December 29, 2021. http://seer.cancer.gov/statfacts/html/breast.html

6. Cardoso F, Spence D, Mertz S, et al. Global analysis of advanced/metastatic breast cancer: Decade report (2005–2015). *Breast*. 2018;39:131-138. doi:10.1016/j.breast.2018.03.002

7. Pe M, Dorme L, Coens C, et al. Statistical analysis of patient-reported outcome data in randomised controlled trials of locally advanced and metastatic breast cancer: a systematic review. *Lancet Oncol*. 2018;19(9):e459-e469. doi:10.1016/S1470-2045(18)30418-2

8. Cardoso F, Cella D, Velikova G, et al. Quality-of-life methodology in hormone receptor–positive advanced breast cancer: Current tools and perspectives for the future. *Cancer Treat Rev*. 2022;102:102321. doi:10.1016/j.ctrv.2021.102321

9. Prat A, Saura C, Pascual T, et al. Ribociclib plus letrozole versus chemotherapy for postmenopausal women with hormone receptor-positive, HER2-negative, luminal B breast cancer (CORALLEEN): an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol*. 2020;21(1):33-43. doi:10.1016/S1470-2045(19)30786-7

10. Clarijs ME, Thurell J, Kühn F, et al. Measuring quality of life using patient-reported outcomes in real-world metastatic breast cancer patients: The need for a standardized approach. *Cancers (Basel)*. 2021;13(10). doi:10.3390/cancers13102308

11. Brédart A, Marrel A, Abetz-Webb L, Lasch K, Acquadro C. Interviewing to develop Patient-Reported Outcome (PRO) measures for clinical research: Eliciting patients' experience. *Health Qual Life Outcomes*. 2014;12(1):1-10. doi:10.1186/1477-7525-12-15

12. Megari K. Quality of life in chronic disease. *Heal Psychol Res*. 2013;27(1):141-148.

doi:10.4081/ijfs.2016.5832

13. Fayers, P; Bottomley A. Quality of life research within the EORTC—the EORTC QLQ-C30. *Eur J Cancer*. 2002;38(4):125-133.

14. Bjelic-Radisic V, Cardoso F, Cameron D, et al. An international update of the EORTC questionnaire for assessing quality of life in breast cancer patients: EORTC QLQ-BR45. *Ann Oncol*. 2020;31(2):283-288. doi:10.1016/j.annonc.2019.10.027

15. Ware Jr, JE; Sherbourne C. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483.

16. Basen-Engquist K, Bodurka-Bevers D, Fitzgerald MA, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Ovarian. *J Clin Oncol*. 2001;19(6):1809-1817. doi:10.1200/JCO.2001.19.6.1809

17. Buchholz I, Janssen MF, Kohlmann T, Feng YS, Balestroni G, Bertolotti G. 121-Article Text-227-1-10-20151201. *Pharmacoeconomics*. 2018;36(6):155-159. https://doi.org/10.1007/s40273-018-0642-5

18. Fayers P, Aaronson N, Bjordal K, et al. EORTC QLQ-C30 Scoring Manual The EORTC QLQ-C30 Introduction. *EORTC QLQ-C30 Scoring Man*. 2001;30:1-67. http://www.eortc.be/qol/files/scmanualqlq-c30.pdf

19. Cox DR, Fitzpatrick R, Fletcher AE, Gore SM, Spiegelhalter DJ JD. Quality-Of-Life Assessment: Can We Keep it Simple? *J R Stat Soc*. 1992;Series A(155):353-393.

20. Arostegui I, Núñez-Antón V, Quintana JM. Statistical approaches to analyse patient-reported outcomes as response variables: An application to health-related quality of life. *Stat Methods Med Res*. 2012;21(2):189-214. doi:10.1177/0962280210379079

21. Verbeke, G; Molenberghs G. *Linear Mixed Models for Longitudinal Data*.; 2000.

22. Najera-Zuloaga J, Lee DJ, Arostegui I. Comparison of beta-binomial regression model approaches to analyze health-related quality of life data. *Stat Methods Med Res*. 2018;27(10):2989-3009. doi:10.1177/0962280217690413

23. Najera-Zuloaga J, Lee DJ, Arostegui I. A beta-binomial mixed-effects model approach for analysing longitudinal discrete and bounded outcomes. *Biometrical J*. 2019;61(3):600-615. doi:10.1002/bimj.201700251

24. Peña D. *Fundamentos de Estadística*.; 2001.

25. Kleinbaum, D. G.; Klein M. *Survival Analysis: A Self-Learning Text*.; 2012.

26. Bottomley A, Reijneveld JC, Koller M, et al. Current state of quality of life and patient-reported outcomes research. *Eur J Cancer*. 2019;121:55-63. doi:10.1016/j.ejca.2019.08.016

27. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): A randomised phase 2 study. *Lancet Oncol*. 2015;16(1):25-35. doi:10.1016/S1470-2045(14)71159-3

28. Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. *N Engl J Med*. 2016;375(20):1925-1936. doi:10.1056/nejmoa1607303

29. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phas. *Lancet Oncol*. 2016;17(4):425-439. doi:10.1016/S1470-2045(15)00613-0

30. Giuliano M, Schettini F, Rognoni C, et al. Endocrine treatment versus chemotherapy in postmenopausal women with hormone receptor-positive, HER2-negative, metastatic breast cancer: a systematic review and network meta-analysis. *Lancet Oncol*. 2019;20(10):1360-1369. doi:10.1016/S1470-2045(19)30420-6

31. Schettini F, Giudici F, Giuliano M, et al. Overall Survival of CDK4/6-Inhibitor-Based Treatments in Clinically Relevant Subgroups of Metastatic Breast Cancer: Systematic Review and Meta-Analysis. *J Natl Cancer Inst*. 2020;112(11):1089-1097. doi:10.1093/jnci/djaa071

32. Cottu P, D'Hondt V, Dureau S, et al. Letrozole and palbociclib versus chemotherapy as neoadjuvant therapy of high-risk luminal breast cancer. *Ann Oncol*. 2018;29(12):2334-2340. doi:10.1093/annonc/mdy448

33. Hurvitz SA, Martin M, Press MF, et al. Potent cell-cycle inhibition and upregulation of immune response with abemaciclib and anastrozole in Neomonarch, phase II neoadjuvant study in HR+/HER2- Breast cancer. *Clin Cancer Res*. 2020;26(3):566-580. doi:10.1158/1078-0432.CCR-19-1425

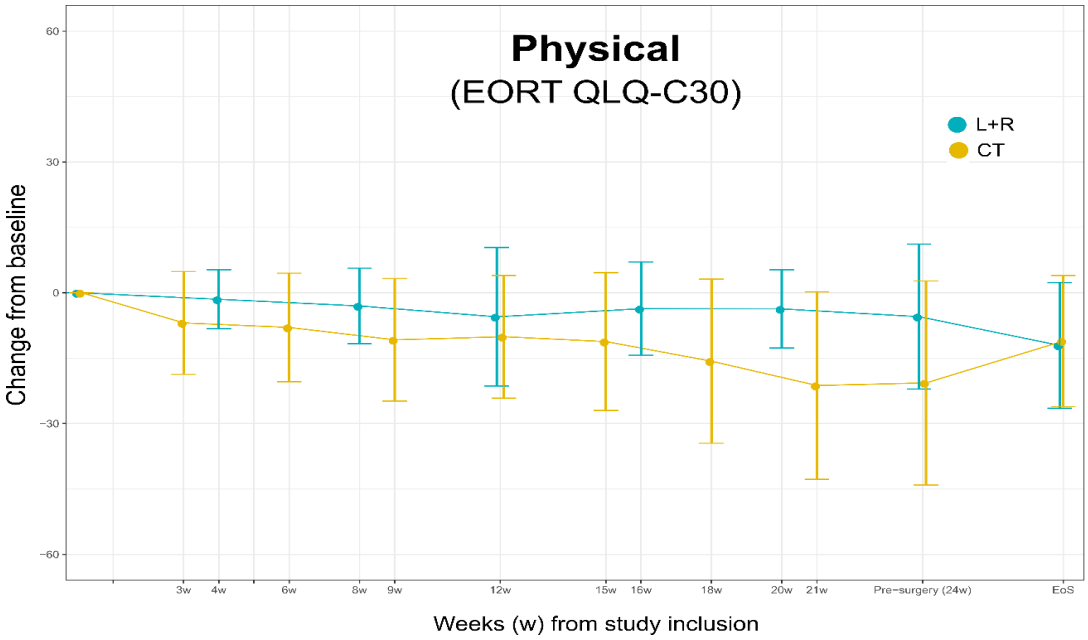
34. Wilcken N, Hornbuckle J, Ghersi D. Chemotherapy or endocrine therapy for metastatic breast cancer? *Breast Cancer Res Treat*. 2003;81(SUPPL. 1). doi:10.1023/a:1026368823440

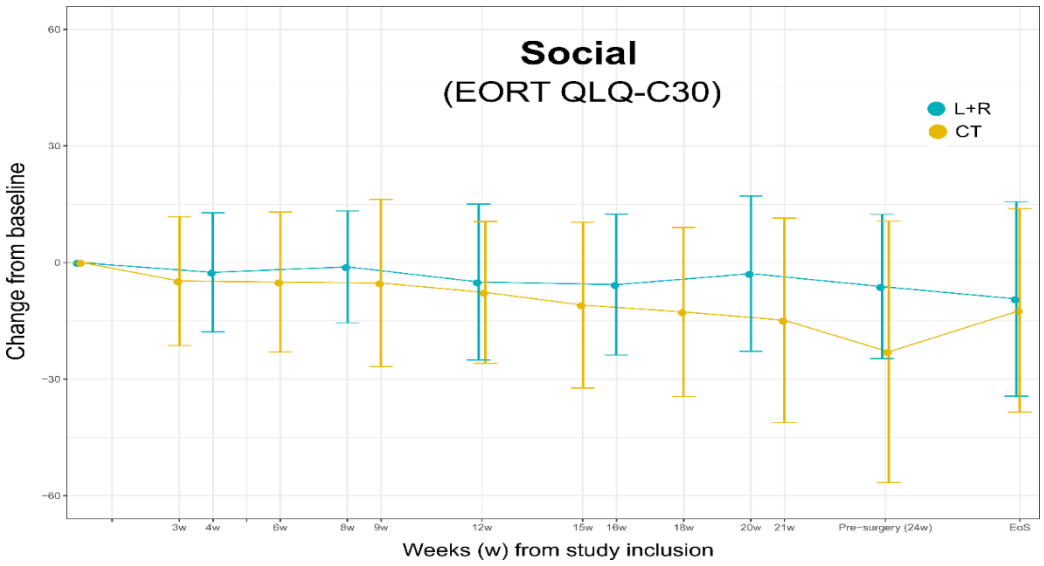
35. Agostinetto E, Vian L, Caparica R, et al. CDK4/6 inhibitors as adjuvant treatment for hormone receptor-positive, HER2-negative early breast cancer: a systematic review and meta-analysis. *ESMO Open*. 2021;6(2):100091. doi:10.1016/j.esmoop.2021.100091

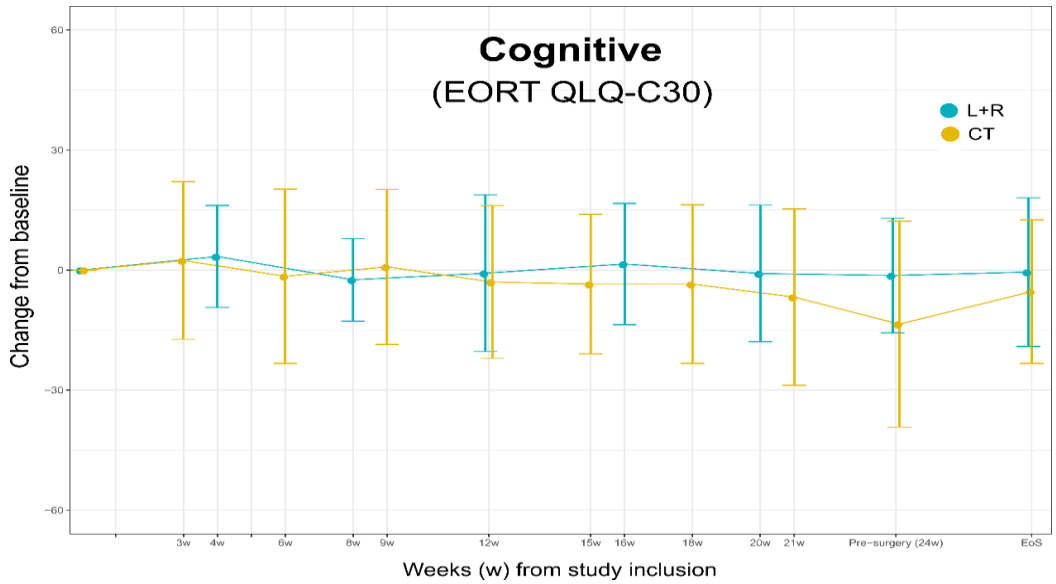
36. Ades F, Zardavas D, Bozovic-Spasojevic I, et al. Luminal B breast cancer: Molecular characterization, clinical management, and future perspectives. *J Clin Oncol*. 2014;32(25):2794-2803. doi:10.1200/JCO.2013.54.1870

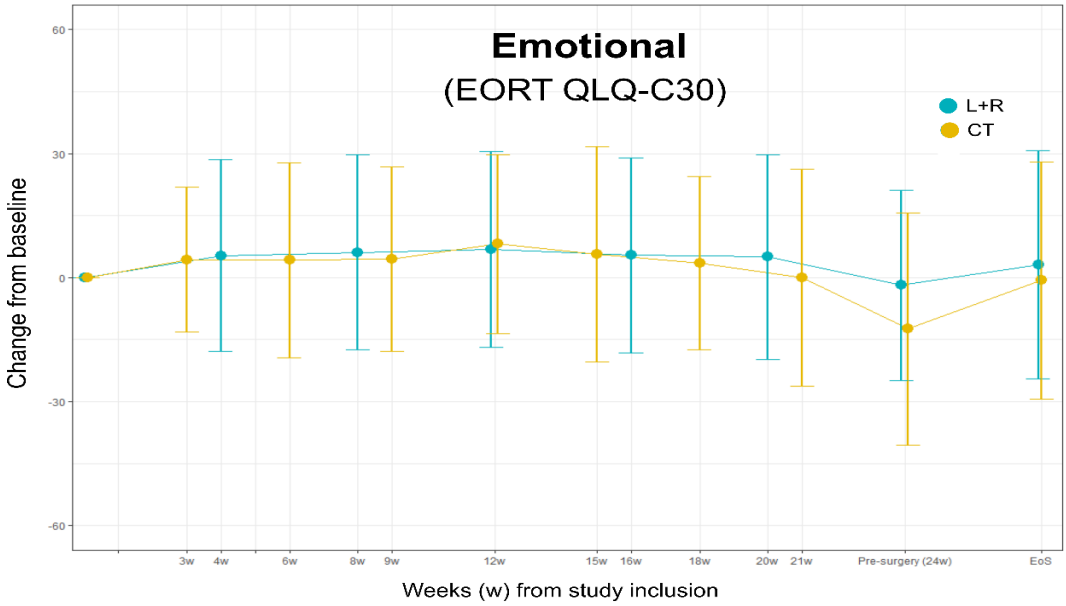
9. Annex

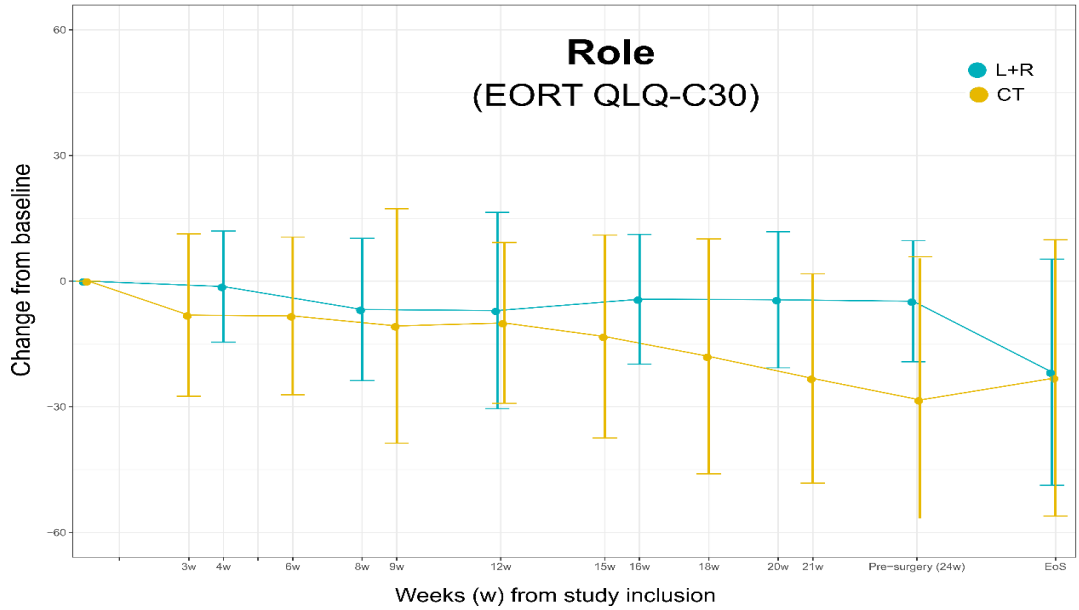
Annex 1 : Evolution of the mean change from baseline values in all functioning scales (along with the mean ± standard deviation) according treatment arm

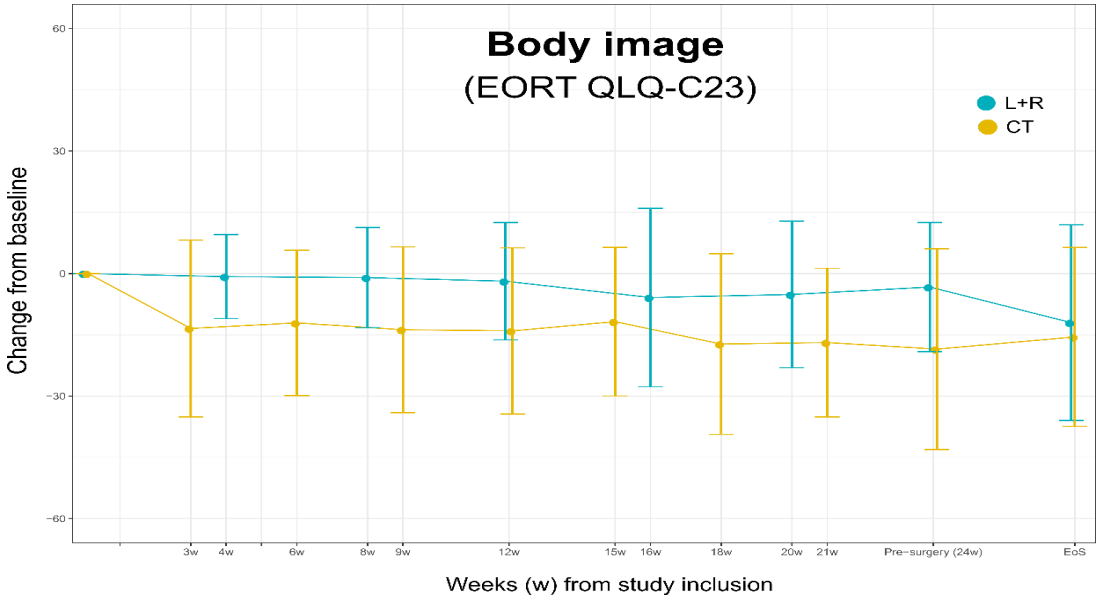


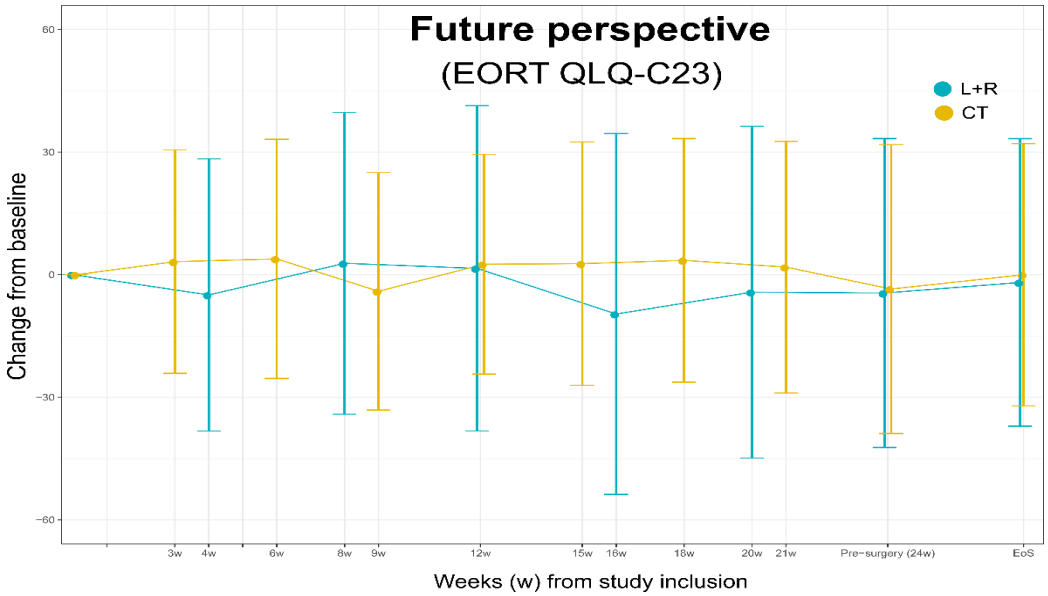


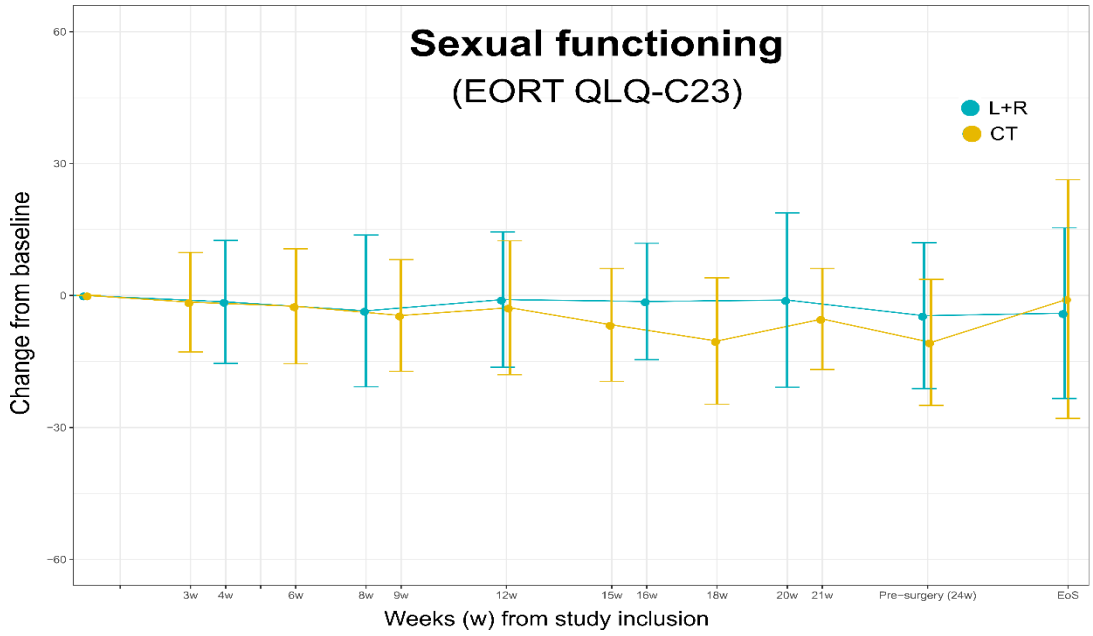

Cognitive
(EORT QLQ-C30)
L+R
CT
Change from baseline
60
30
0
−30
−60
3w
4w
6w
8w
9w
12w
15w
16w
18w
20w
21w
Pre−surgery (24w)
EoS
Weeks (w) from study inclusion

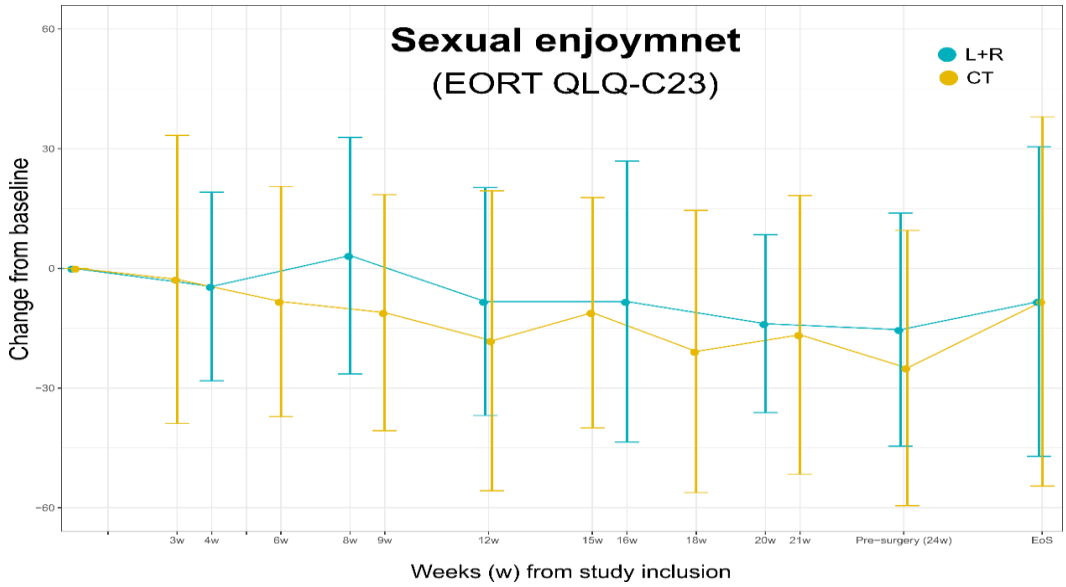

Emotional
(EORT QLQ-C30)
L+R
CT
Change from baseline
60
30
0
-30
-60
3w
4w
6w
8w
9w
12w
15w
16w
18w
20w
21w
Pre−surgery (24w)
EoS
Weeks (w) from study inclusion


Role
(EORT QLQ-C30)
L+R
CT
Change from baseline
60
30
0
−30
−60
3w
4w
6w
8w
9w
12w
15w
16w
18w
20w
21w
Pre−surgery (24w)
EoS
Weeks (w) from study inclusion

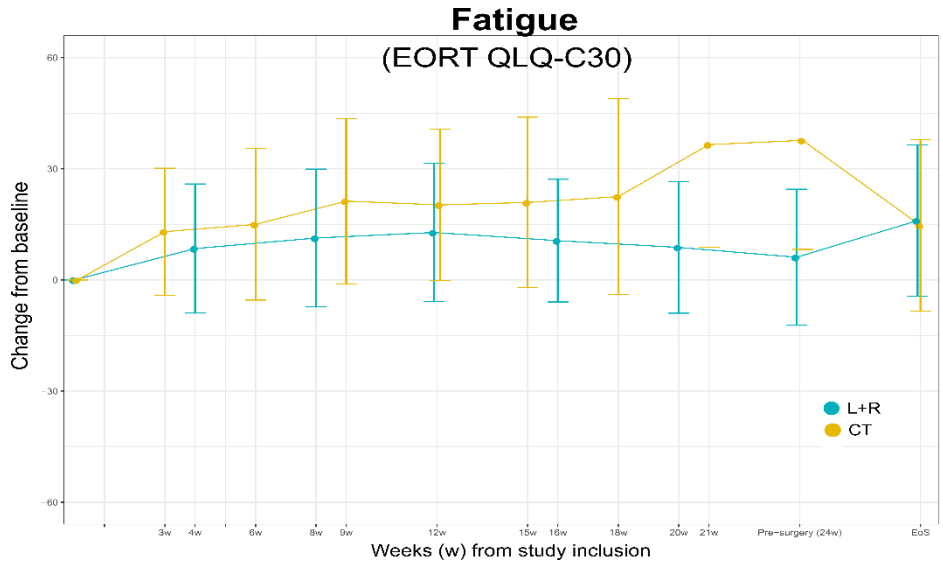

Body image
(EORT QLQ-C23)
L+R
CT
Change from baseline
60
30
0
−30
−60
3w
4w
6w
8w
9w
12w
15w
16w
18w
20w
21w
Pre−surgery (24w)
EoS
Weeks (w) from study inclusion

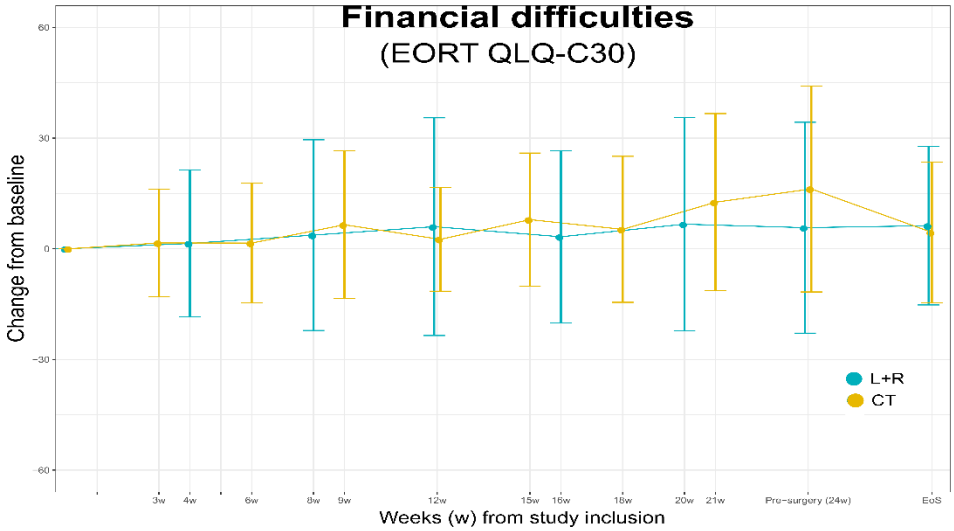

Future perspective
(EORT QLQ-C23)
L+R
CT
Change from baseline
60
30
0
−30
−60
3w
4w
6w
8w
9w
12w
15w
16w
18w
20w
21w
Pre−surgery (24w)
EoS
Weeks (w) from study inclusion

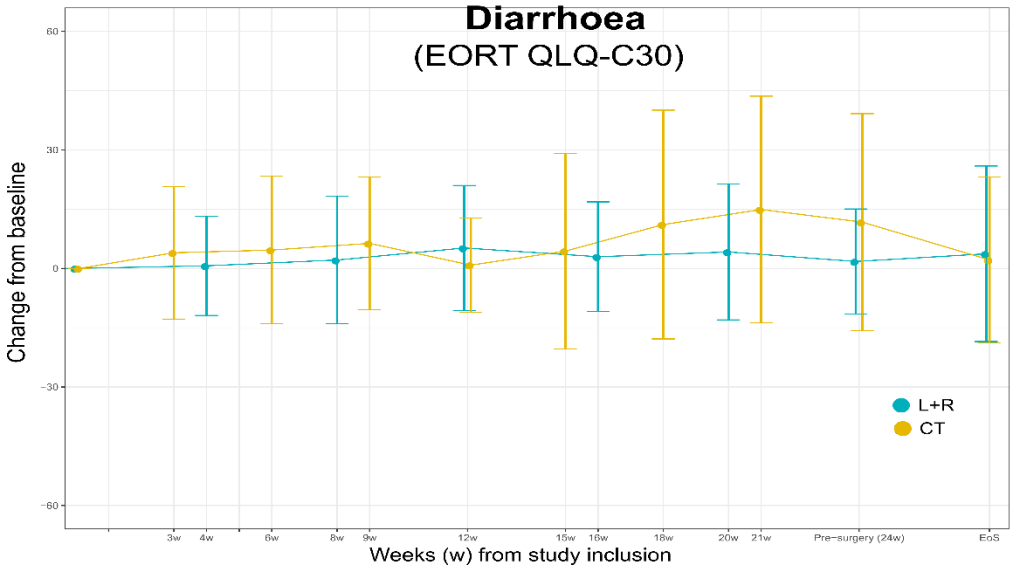

Sexual functioning
(EORT QLQ-C23)
L+R
CT
Change from baseline
60
30
0
−30
−60
3w
4w
6w
8w
9w
12w
15w
16w
18w
20w
21w
Pre−surgery (24w)
EoS
Weeks (w) from study inclusion

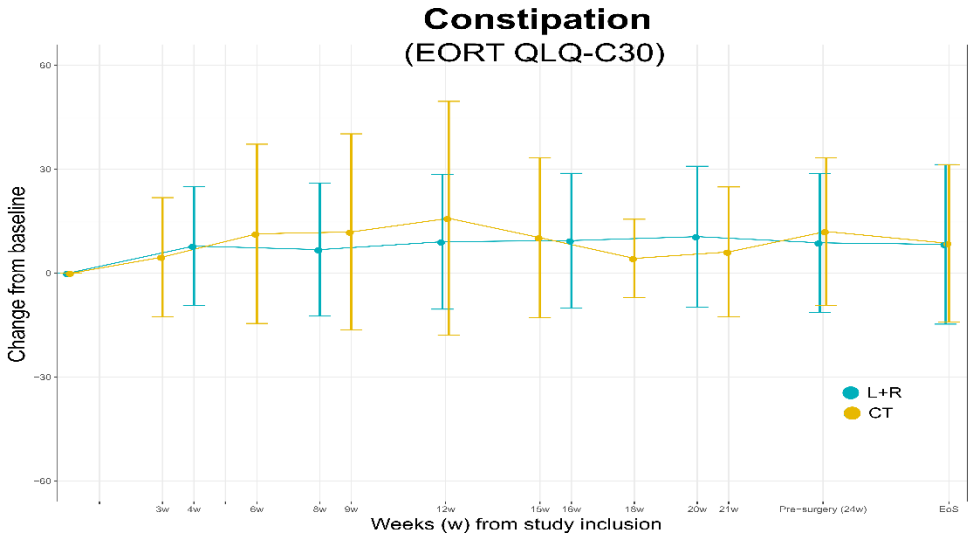

Sexual enjoymnet
(EORT QLQ-C23)
L+R
CT
Change from baseline
60
30
0
−30
−60
3w
4w
6w
8w
9w
12w
15w
16w
18w
20w
21w
Pre−surgery (24w)
EoS
Weeks (w) from study inclusion

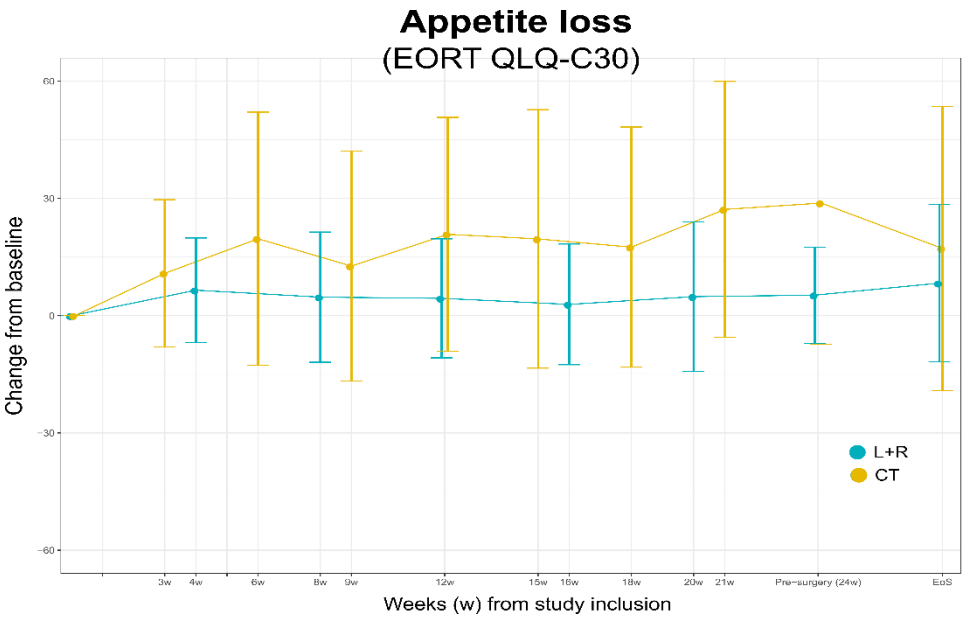
Annex 2 : Evolution of the mean change from baseline values in all symptom scales (along with the mean ± standard deviation) according treatment arm

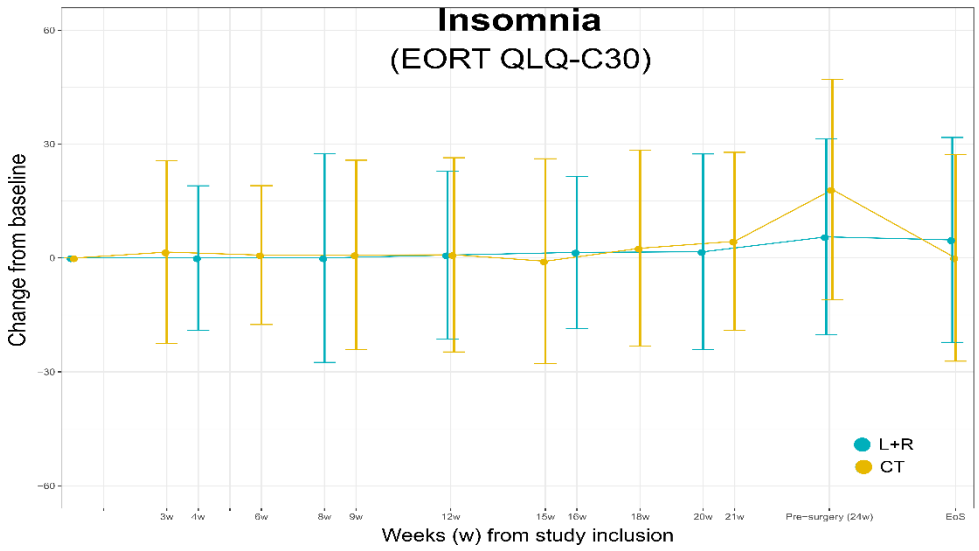


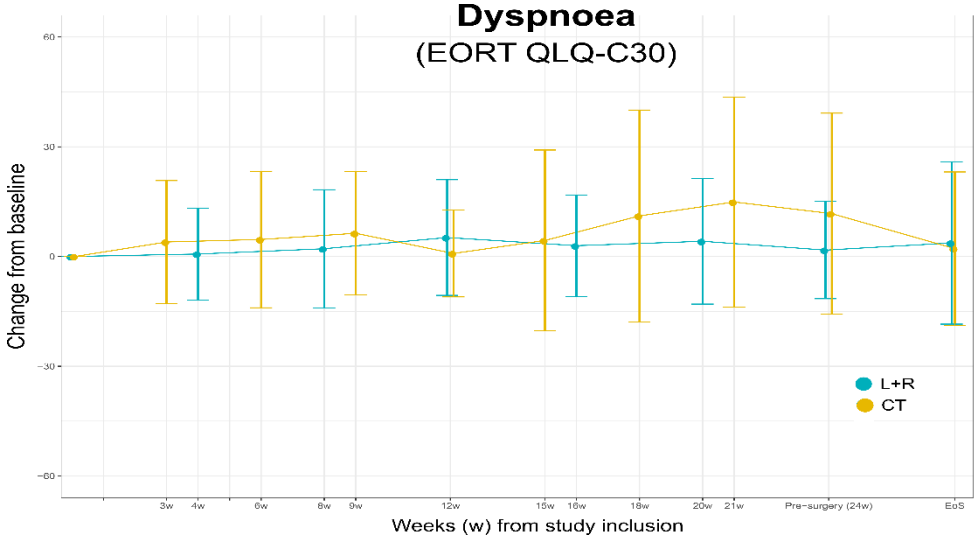


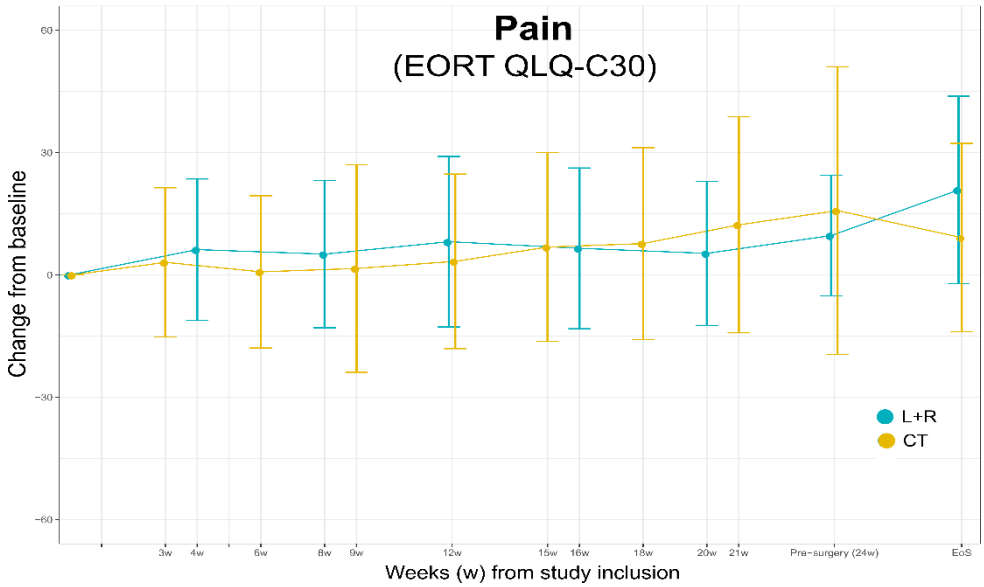

Diarrhoea
(EORT QLQ-C30)
Change from baseline
60
30
0
−30
−60
L+R
CT
3w
4w
6w
8w
9w
12w
15w
16w
18w
20w
21w
Pre−surgery (24w)
EoS
Weeks (w) from study inclusion

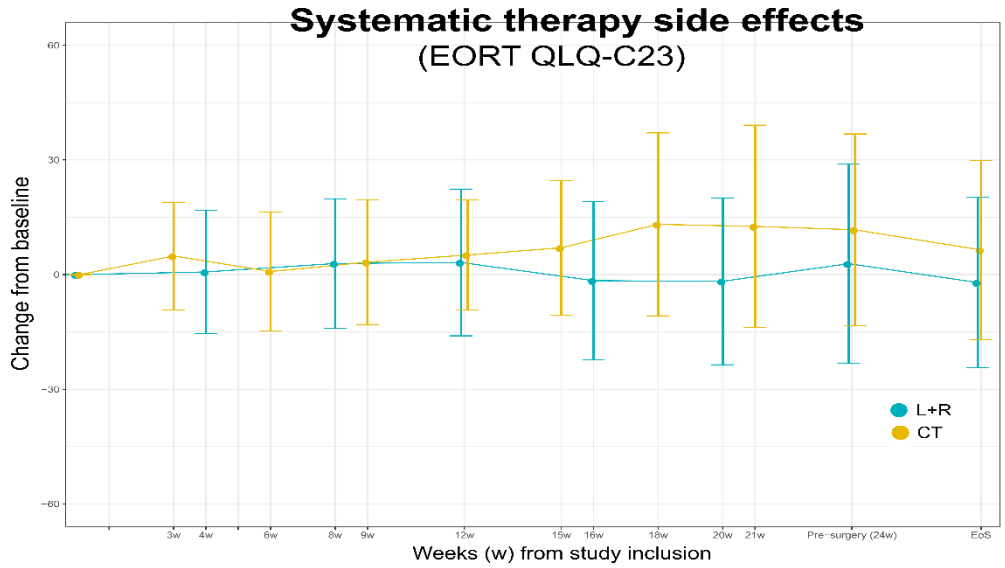

Constipation
(EORT QLQ-C30)
Change from baseline
60
30
0
−30
−60
L+R
CT
3w
4w
6w
8w
9w
12w
15w
16w
18w
20w
21w
Pre−surgery (24w)
EoS
Weeks (w) from study inclusion

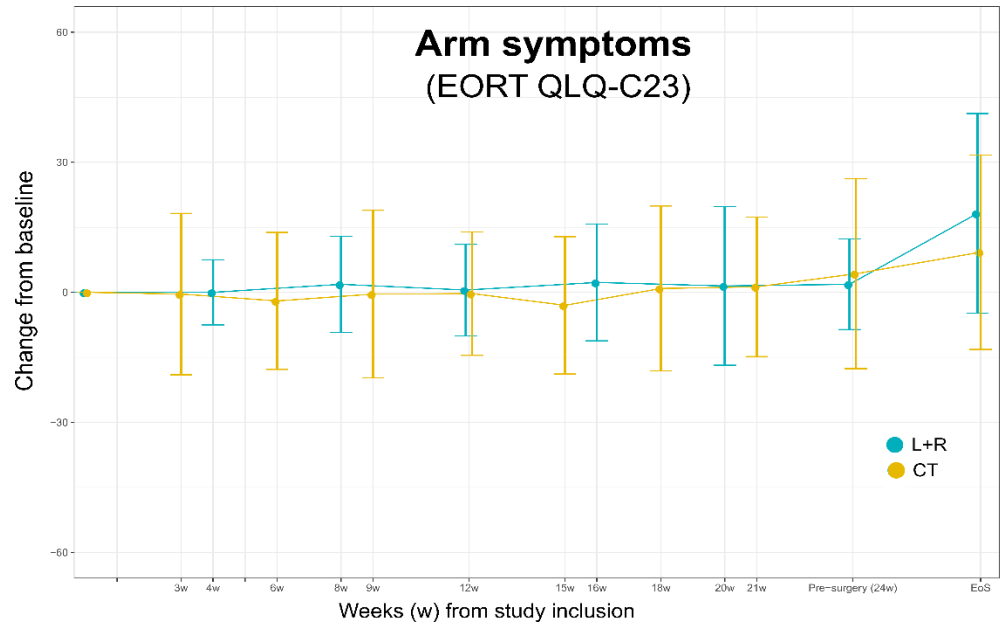

Appetite loss
(EORT QLQ-C30)
Change from baseline
60
30
0
−30
−60
L+R
CT
3w
4w
6w
8w
9w
12w
15w
16w
18w
20w
21w
Pre−surgery (24w)
EoS
Weeks (w) from study inclusion

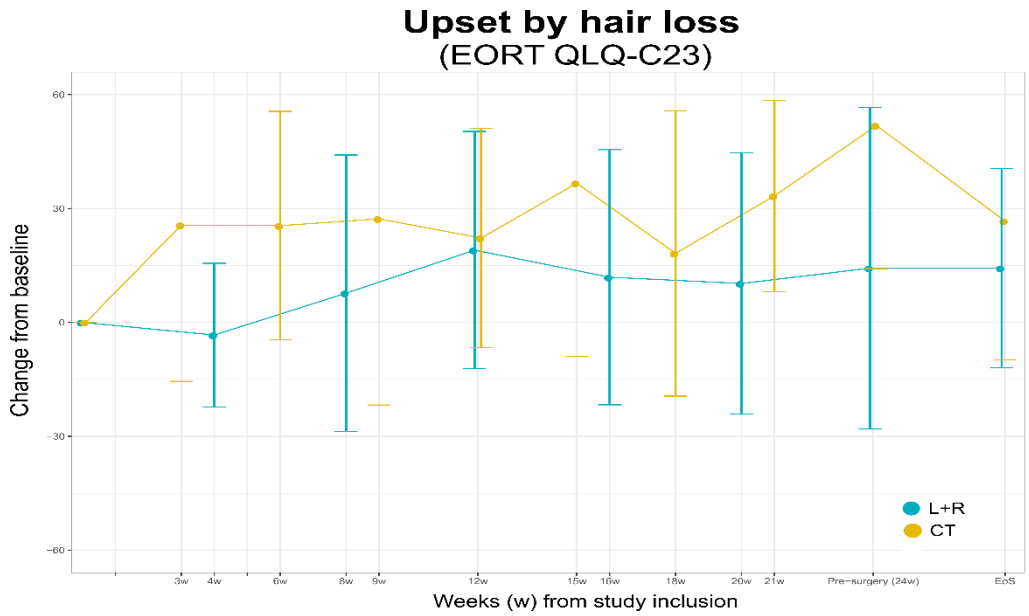

Insomnia
(EORT QLQ-C30)
Change from baseline
60
30
0
−30
−60
L+R
CT
3w
4w
6w
8w
9w
12w
15w
16w
18w
20w
21w
Pre−surgery (24w)
EoS
Weeks (w) from study inclusion

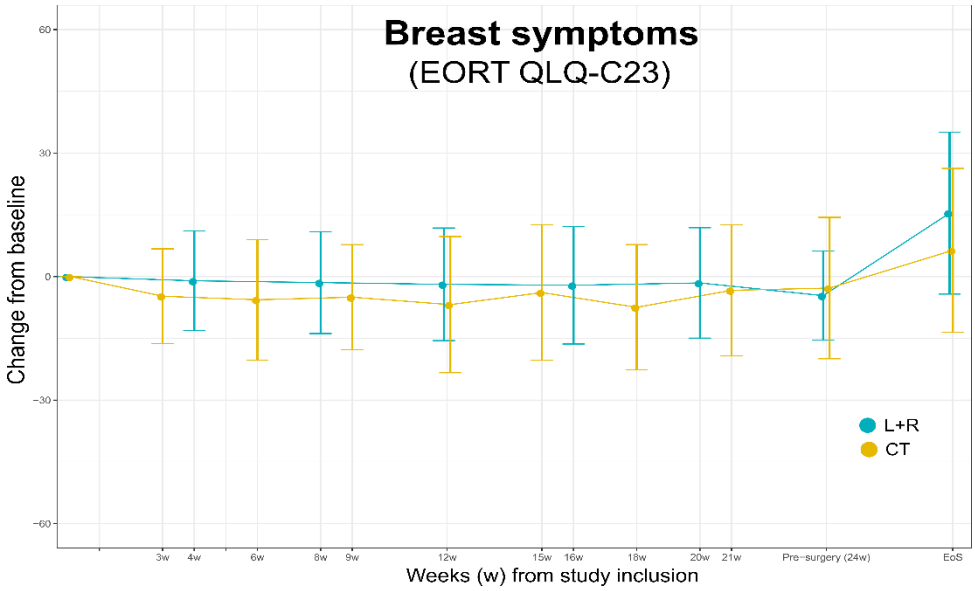

Dyspnoea
(EORT QLQ-C30)
Change from baseline
60
30
0
−30
−60
L+R
CT
3w
4w
6w
8w
9w
12w
15w
16w
18w
20w
21w
Pre−surgery (24w)
EoS
Weeks (w) from study inclusion


Pain
(EORT QLQ-C30)
Change from baseline
60
30
0
−30
−60
L+R
CT
3w
4w
6w
8w
9w
12w
15w
16w
18w
20w
21w
Pre−surgery (24w)
EoS
Weeks (w) from study inclusion


Systematic therapy side effects
(EORT QLQ-C23)
Change from baseline
60
30
0
−30
−60
L+R
CT
3w
4w
6w
8w
9w
12w
15w
16w
18w
20w
21w
Pre−surgery (24w)
EoS
Weeks (w) from study inclusion


Arm symptoms
(EORT QLQ-C23)
Change from baseline
60
30
0
−30
−60
L+R
CT
3w
4w
6w
8w
9w
12w
15w
16w
18w
20w
21w
Pre−surgery (24w)
EoS
Weeks (w) from study inclusion


Upset by hair loss
(EORT QLQ-C23)
Change from baseline
60
30
0
−30
−60
L+R
CT
3w
4w
6w
8w
9w
12w
15w
16w
18w
20w
21w
Pre−surgery (24w)
EoS
Weeks (w) from study inclusion


Breast symptoms
(EORT QLQ-C23)
Change from baseline
60
30
0
−30
−60
3w
4w
6w
8w
9w
12w
15w
16w
18w
20w
21w
Pre−surgery (24w)
EoS
Weeks (w) from study inclusion
L+R
CT

Annex 3 : R code

```
#################################
### Treball final de máster (TFM)
#################################

### Coralleen trial: Quality of life analysis

#####################
### 0. Pre-processing
#####################
# setwd("C:/Users/gvillacampa/Dropbox/VHIO/SOLTI/CORALLEEN/bbdd")
library(survival)
library(dplyr)
library(ggplot2)
library(lme4)
library(fmsb)
dat <- read.csv("CORALLEEN_QoL.csv",dec=",")
tfm <- subset(dat,select=c(ID.patient,Arm,Visita,Day.of.visit,Global.health.status,Physical.functioning,Role.functioning,
                Emotional.functioning,Cognitive.functioning,Social.functioning,Fatigue,Nausea.and.vomiting,
                Pain,Dyspnoea,Insomnia,Appetite.loss,Constipation,Diarrhoea,Financial.difficulties,
                Body.image,Sexual.functioning,Sexual.enjoyment,Future.perspective,Systemictherapysideeffects,
                Breast.symptoms,Arm.symptoms,Upset.by.hair.loss))


##### Calculation of change from baseline
dat  <- dat %>% mutate_at(c("Day.of.visit"), as.Date, format="%d/%m/%Y")
dat$dif <- NA
dat$global_change <- NA
dat$pain_new <- NA
dat$physical_f <- NA
dat$role_f <- NA
dat$emotional_f <- NA
dat$cognitive_f <- NA
dat$social_f <- NA
dat$fatigue_new <- NA
dat$nausea_new <- NA
dat$dyspnoea_new <- NA
dat$insomnia_new <- NA
dat$appetite_new <- NA
dat$constipation_new <- NA
dat$diarrhoea_new <- NA
dat$financial_new <- NA
dat$body <- NA
dat$sexual_function <- NA
dat$sexual_enjoyment <- NA
dat$breast_simp <- NA
dat$hair_new <- NA
dat$future_function <- NA
dat$systematic_side <- NA
dat$arm_symptom <- NA

dat$Systemictherapysideeffects
dat$Arm.symptoms

j <- levels(dat$ID.patient)
i<-1
for (i in 1:length(j)){
  dat$dif[dat$ID.patient==j[i]] <-round(as.numeric(dat$Day.of.visit[dat$ID.patient==j[i]]- dat$Day.of.visit[dat$ID.patient==j[i]][1] )/7,1)
  dat$global_change[dat$ID.patient==j[i]] <-round(as.numeric(dat$Global.health.status[dat$ID.patient==j[i]]-
dat$Global.health.status[dat$ID.patient==j[i]][1]),1)
  if (is.na(dat$Global.health.status[dat$ID.patient==j[i]][1])){
    dat$global_change[dat$ID.patient==j[i]] <-round(as.numeric(dat$Global.health.status[dat$ID.patient==j[i]]-
dat$Global.health.status[dat$ID.patient==j[i]][!is.na(dat$Global.health.status[dat$ID.patient==j[i]])][1]),1)
  }
```

```
 dat$global[dat$ID.patient==j[i]] <-round(as.numeric(dat$Global.health.status[dat$ID.patient==j[i]]-
dat$Global.health.status[dat$ID.patient==j[i]][1] ),1)
 dat$pain_new[dat$ID.patient==j[i]] <-round(as.numeric(dat$Pain[dat$ID.patient==j[i]]- dat$Pain[dat$ID.patient==j[i]][1] ),1)
 dat$physical_f[dat$ID.patient==j[i]] <-round(as.numeric(dat$Physical.functioning[dat$ID.patient==j[i]]-
dat$Physical.functioning[dat$ID.patient==j[i]][1] ),1)
 dat$role_f[dat$ID.patient==j[i]] <-round(as.numeric(dat$Role.functioning[dat$ID.patient==j[i]]-
dat$Role.functioning[dat$ID.patient==j[i]][1] ),1)
 dat$emotional_f[dat$ID.patient==j[i]] <-round(as.numeric(dat$Emotional.functioning[dat$ID.patient==j[i]]-
dat$Emotional.functioning[dat$ID.patient==j[i]][1] ),1)
 dat$cognitive_f[dat$ID.patient==j[i]] <-round(as.numeric(dat$Cognitive.functioning[dat$ID.patient==j[i]]-
dat$Cognitive.functioning[dat$ID.patient==j[i]][1] ),1)
 dat$social_f[dat$ID.patient==j[i]] <-round(as.numeric(dat$Social.functioning[dat$ID.patient==j[i]]-
dat$Social.functioning[dat$ID.patient==j[i]][1] ),1)
 dat$fatigue_new[dat$ID.patient==j[i]] <-round(as.numeric(dat$Fatigue[dat$ID.patient==j[i]]- dat$Fatigue[dat$ID.patient==j[i]][1] ),1)
 dat$nausea_new[dat$ID.patient==j[i]] <-round(as.numeric(dat$Nausea.and.vomiting[dat$ID.patient==j[i]]-
dat$Nausea.and.vomiting[dat$ID.patient==j[i]][1] ),1)
 dat$dyspnoea_new[dat$ID.patient==j[i]] <-round(as.numeric(dat$Dyspnoea[dat$ID.patient==j[i]]- dat$Dyspnoea[dat$ID.patient==j[i]][1]
),1)
 dat$insomnia_new[dat$ID.patient==j[i]] <-round(as.numeric(dat$Insomnia[dat$ID.patient==j[i]]- dat$Insomnia[dat$ID.patient==j[i]][1]
),1)
 dat$appetite_new[dat$ID.patient==j[i]] <-round(as.numeric(dat$Appetite.loss[dat$ID.patient==j[i]]-
dat$Appetite.loss[dat$ID.patient==j[i]][1] ),1)
 dat$constipation_new[dat$ID.patient==j[i]] <-round(as.numeric(dat$Constipation[dat$ID.patient==j[i]]-
dat$Constipation[dat$ID.patient==j[i]][1] ),1)
 dat$diarrhoea_new[dat$ID.patient==j[i]] <-round(as.numeric(dat$Diarrhoea[dat$ID.patient==j[i]]- dat$Diarrhoea[dat$ID.patient==j[i]][1]
),1)
 dat$financial_new[dat$ID.patient==j[i]] <-round(as.numeric(dat$Financial.difficulties[dat$ID.patient==j[i]]-
dat$Financial.difficulties[dat$ID.patient==j[i]][1] ),1)
 dat$body[dat$ID.patient==j[i]] <-round(as.numeric(dat$Body.image[dat$ID.patient==j[i]]- dat$Body.image[dat$ID.patient==j[i]][1] ),1)
 dat$sexual_function[dat$ID.patient==j[i]] <-round(as.numeric(dat$Sexual.functioning[dat$ID.patient==j[i]]-
dat$Sexual.functioning[dat$ID.patient==j[i]][1] ),1)
 dat$sexual_enjoyment[dat$ID.patient==j[i]] <-round(as.numeric(dat$Sexual.enjoyment[dat$ID.patient==j[i]]-
dat$Sexual.enjoyment[dat$ID.patient==j[i]][1] ),1)
 dat$breast_simp[dat$ID.patient==j[i]] <-round(as.numeric(dat$Breast.symptoms[dat$ID.patient==j[i]]-
dat$Breast.symptoms[dat$ID.patient==j[i]][1] ),1)
 dat$hair_new[dat$ID.patient==j[i]] <-round(as.numeric(dat$Upset.by.hair.loss[dat$ID.patient==j[i]]-
dat$Upset.by.hair.loss[dat$ID.patient==j[i]][1] ),1)
 dat$future_function[dat$ID.patient==j[i]] <-round(as.numeric(dat$Future.perspective[dat$ID.patient==j[i]]-
dat$Future.perspective[dat$ID.patient==j[i]][1] ),1)
dat$arm_symptom[dat$ID.patient==j[i]] <-round(as.numeric(dat$Arm.symptoms[dat$ID.patient==j[i]]-
dat$Arm.symptoms[dat$ID.patient==j[i]][1] ),1)
 dat$systematic_side[dat$ID.patient==j[i]] <-round(as.numeric(dat$Systemictherapysideeffects[dat$ID.patient==j[i]]-
dat$Systemictherapysideeffects[dat$ID.patient==j[i]][1] ),1)

}
dat$Systemictherapysideeffects

##### Filter for evaluations that are no NA (only available information approach)
qol <- subset(dat, !is.na(X1.Doyouhaveanytroubledoingstrenuousactivities.likecarryingaheavyshoppingbagorasuitcase.))
qol <- subset(qol,qol$X31.Didyouhaveadrymouth!=5 | !is.na(Global.health.status) )
qol <- subset(dat,!is.na(Global.health.status))
qol$Visita <- as.character(qol$Visita)

for (i in 1:nrow(qol)){

 if(qol$Arm[i]=="Letro+Ribo" & is.na(qol$Visita[i])){
  qol$Visita[i] <- ifelse(qol$dif[i]< 6,"1.Week4",ifelse(qol$dif[i]>= 6 & qol$dif[i]<10,"2.Week8",
                                  ifelse(qol$dif[i]>= 10 & qol$dif[i]<14,"3.Week12",ifelse(qol$dif[i]>= 14 & qol$dif[i]<18,"4.Week16",
                                                                  ifelse(qol$dif[i]>= 18 & qol$dif[i]<22,"5.Week20",ifelse(qol$dif[i]>= 22 &
qol$dif[i]<26,"6.Week24"))))))

 }

 if(qol$Arm[i]=="AC+pacli" & is.na(qol$Visita[i])){
  qol$Visita[i] <- ifelse(qol$dif[i]< 4.5,"1.Week3",ifelse(qol$dif[i]>= 4.5 & qol$dif[i]<7.5,"2.Week6",
```

```
                                    ifelse(qol$dif[i]>= 7.5 & qol$dif[i]<10.5,"3.Week9",ifelse(qol$dif[i]>= 10.5 & qol$dif[i]<13.5,"4.Week12",
                                                                                               ifelse(qol$dif[i]>= 13.5 & qol$dif[i]<16.5,"5.Week15",ifelse(qol$dif[i]>=
16.5 & qol$dif[i]<19.5,"6.Week18",
                                                                                                                                            ifelse(qol$dif[i]>= 19.5 &
qol$dif[i]<=24,"7.Week21")))))))

  }

}
qol$X29.Howwouldyourateyouroverallhealthduringthepastweek[qol$X29.Howwouldyourateyouroverallhealthduringthepastweek==8] <-
NA
qol$X30.Howwouldyourateyouroverallqualityoflifeduringthepastweek[qol$X30.Howwouldyourateyouroverallqualityoflifeduringthepastwe
ek==8]<- NA
qol$global_value <- (qol$X29.Howwouldyourateyouroverallhealthduringthepastweek+
qol$X30.Howwouldyourateyouroverallqualityoflifeduringthepastweek)/2
qol$global_value2 <- qol$X29.Howwouldyourateyouroverallhealthduringthepastweek+
qol$X30.Howwouldyourateyouroverallqualityoflifeduringthepastweek
qol$Visita[qol$ID.patient=="1016-030"] <- c("0.Week1","1.Week3","2.Week6","3.Week9",
"4.Week12","5.Week15","6.Week18","7.Week21","Pre-surgery","z_EoS")
qol$Visita[qol$Visita=="Week1"] <- "0.Week1"
qol$Visita[qol$Visita=="EoS"] <- "z_EoS"

ribo <- subset(qol, Arm=="Letro+Ribo")
ct <- subset(qol, Arm=="AC+pacli")


###################################
### Compliance rates
###################################

baseline <- subset(dat, Visita=="Week1")
ribo <- subset(dat, c(Visita=="Week1",Arm=="Letro+Ribo"))
ct <- subset(dat, c(Visita=="Week1",Arm=="AC+pacli"))
table(baseline$Global.health.status)

length(baseline$Global.health.status[!is.na(baseline$Global.health.status)])
length(baseline$Physical.functioning[!is.na(baseline$Physical.functioning)])
length(baseline$Role.functioning[!is.na(baseline$Role.functioning)])
length(baseline$Emotional.functioning[!is.na(baseline$Emotional.functioning)])
length(baseline$Cognitive.functioning[!is.na(baseline$Cognitive.functioning)])
length(baseline$Social.functioning[!is.na(baseline$Social.functioning)])

length(baseline$Fatigue[!is.na(baseline$Fatigue)])
length(baseline$Nausea.and.vomiting[!is.na(baseline$Nausea.and.vomiting)])
length(baseline$Pain[!is.na(baseline$Pain)])
length(baseline$Dyspnoea[!is.na(baseline$Dyspnoea)])
length(baseline$Insomnia[!is.na(baseline$Insomnia)])
length(baseline$Appetite.los[!is.na(baseline$Appetite.los)])
length(baseline$Constipation[!is.na(baseline$Constipation)])
length(baseline$Diarrhoea[!is.na(baseline$Diarrhoea)])
length(baseline$Financial.difficulties[!is.na(baseline$Financial.difficulties)])

length(baseline$Body.image[!is.na(baseline$Body.image)])
length(baseline$Sexual.functioning[!is.na(baseline$Sexual.functioning)])
length(baseline$Sexual.enjoyment[!is.na(baseline$Sexual.enjoyment)])
length(baseline$Future.perspective[!is.na(baseline$Future.perspective)])
length(baseline$Systemictherapysideeffects[!is.na(baseline$Systemictherapysideeffects)])
length(baseline$Breast.symptoms[!is.na(baseline$Breast.symptoms)])
length(baseline$Arm.symptoms[!is.na(baseline$Arm.symptoms)])
length(baseline$Upset.by.hair.loss[!is.na(baseline$Upset.by.hair.loss)])
length(baseline$Sexual.enjoyment[!is.na(baseline$Sexual.enjoyment)])


#########################
### 5.2.1 Baseline scores
#########################
```

```
x0 <- tapply(baseline$Global.health.status, baseline$Arm,mean,na.rm=T)
tapply(baseline$global_ordinal, baseline$Arm,mean,na.rm=T)

windows(20,24)
boxplot(baseline$Global.health.status~ baseline$Arm, ylim=c(0, 100))
ggplot(baseline, aes(x=Arm, y=Global.health.status)) +  geom_violin(trim=FALSE, fill="#FC8D62", color="darkred",width = 0.7)+
  ylim(0, 100)+ geom_boxplot(width=0.1)+ theme_minimal()


windows(20,16)
hist(baseline$Global.health.status, breaks=20, xlim=c(0,100), ylim=c(0,30), las=1, main="Global health status (score 0-100)",
    ylab="Frequency (n)",xlab="Global health status scores", cex.lab=1.5, cex.main=2,cex.axis=1.3,col="grey80" )

baseline$global_ordinal <- ifelse(baseline$X29.HowwouldyourateyouroverallhealthduringthepastweekNA,
                          baseline$X29.Howwouldyourateyouroverallhealthduringthepastweek) +
                      ifelse(baseline$X30.Howwouldyourateyouroverallqualityoflifeduringthepastweek==8,NA,
                          baseline$X30.Howwouldyourateyouroverallqualityoflifeduringthepastweek)

windows(20,16)
hist(baseline$global_ordinal,  xlim=c(0,14), ylim=c(0,30), las=1, main="Global health status (score 0-14)",
    ylab="Frequency (n)",xlab="Global health status scores", cex.lab=1.5, cex.main=2,cex.axis=1.3,col="grey80" )


second <- subset(qol, c(Visita=="1.Week3"|Visita=="1.Week4"))
windows(20,16)
hist(second$global_change,  xlim=c(-100,100), ylim=c(0,50), breaks=16,las=1, main="Change from baseline (score 0-100)",
    ylab="Frequency (n)",xlab="Global health status scores", cex.lab=1.5, cex.main=2,cex.axis=1.3,col="grey80" )


windows(20,16)
hist(baseline$global_ordinal,  xlim=c(0,14), ylim=c(0,30), las=1, main="Global health status (score 0-14)",
    ylab="Frequency (n)",xlab="Global health status scores", cex.lab=1.5, cex.main=2,cex.axis=1.3,col="grey80" )

windows(20,24)
boxplot(baseline$Global.health.status~ baseline$Arm,  las=1,ylim=c(0, 100),frame=F,outline=FALSE,main="Global health status (score 0-
100)",
      ylab="Frequency (n)",cex.lab=1.4, cex.main=1.5,cex.axis=1.5,col="grey80",xlab="Treatment",names=c("CT","L+R"))

stripchart(baseline$Global.health.status~ baseline$Arm,jitter=0.07, method = "jitter",add=T,
        vertical = TRUE,at=c(1,2),pch=19,cex=1.4,bg=1,col=c("#E7B800","#00AFBB"))

windows(20,24)
boxplot(baseline$global_ordinal ~ baseline$Arm,  las=1,ylim=c(0, 14),frame=F,outline=FALSE,main="Global health status (score 0-14)",
      ylab="Frequency (n)",cex.lab=1.4, cex.main=1.5,cex.axis=1.5,col="grey80",xlab="Treatment",names=c("CT","L+R"))

stripchart(baseline$global_ordinal ~ baseline$Arm,jitter=0.07, method = "jitter",add=T,
        vertical = TRUE,at=c(1,2),pch=19,cex=1.4,bg=1,col=c("#E7B800","#00AFBB"))


################################################
### 5.2.2 Baseline scores: Functioning scales
################################################

x1 <- tapply(baseline$Physical.functioning, baseline$Arm,mean,na.rm=T)
x2 <- tapply(baseline$Role.functioning, baseline$Arm,mean,na.rm=T)
x3 <- tapply(baseline$Emotional.functioning, baseline$Arm,mean,na.rm=T)
x4 <- tapply(baseline$Cognitive.functioning, baseline$Arm,mean,na.rm=T)
x5 <- tapply(baseline$Social.functioning, baseline$Arm,mean,na.rm=T)
x<- as.data.frame(matrix( c(x1,x2,x3,x4,x5) , ncol=5))
colnames(x) <- c("Physical" , "Role" , "Emotional " ,
                 "Cognitive" , "Social " )
data <- rbind(rep(100,5) , rep(0,5) , x)

mypal <-  c( "#E7B800","#00AFBB")
windows(20,14)
```

```
radarchart(data,plty=1,plwd=4,pcol=mypal,cglty=1,cglcol="grey60",axistype=1,axislabcol="grey50",
        caxislabels=c(0,25,50,75,100))

x6 <- tapply(baseline$Body.image, baseline$Arm,mean,na.rm=T)
x7 <- tapply(baseline$Sexual.functioning, baseline$Arm,mean,na.rm=T)
x8 <- tapply(baseline$Sexual.enjoyment, baseline$Arm,mean,na.rm=T)
x9 <- tapply(baseline$Future.perspective, baseline$Arm,mean,na.rm=T)


x<- as.data.frame(matrix( c(x6,x7,x8,x9) , ncol=4))
colnames(x) <- c("Body image" , "Sexual functioning" , "Sexual enjoyment" ,
             "Future perspective")
data <- rbind(rep(100,4) , rep(0,4) , x)


windows(20,14)
radarchart(data,plty=1,plwd=4,pcol=mypal,cglty=1,cglcol="grey60",axistype=1,axislabcol="grey50",
        caxislabels=c(0,25,50,75,100))

##############################################
### 5.2.3 Baseline scores: Symptom scales
##############################################

y0 <- tapply(baseline$Fatigue, baseline$Arm,mean,na.rm=T)
y1 <- tapply(baseline$Nausea.and.vomiting, baseline$Arm,mean,na.rm=T)
y2 <- tapply(baseline$Pain, baseline$Arm,mean,na.rm=T)
y3 <- tapply(baseline$Dyspnoea, baseline$Arm,mean,na.rm=T)
y4 <- tapply(baseline$Insomnia, baseline$Arm,mean,na.rm=T)
y5 <- tapply(baseline$Appetite.loss, baseline$Arm,mean,na.rm=T)
y6 <- tapply(baseline$Constipation, baseline$Arm,mean,na.rm=T)
y7 <- tapply(baseline$Diarrhoea, baseline$Arm,mean,na.rm=T)
y8 <- tapply(baseline$Financial.difficulties, baseline$Arm,mean,na.rm=T)

x<- as.data.frame(matrix( c(y0,y1,y2,y3,y4,y5,y6,y7,y8) , ncol=9))
colnames(x) <- c("Fatigue" , "Nausea and vomiting" , "Pain" ,
              "Dyspnoea" , "Insomnia","Appetite loss" , "Constipation","Diarrhoea","Financial difficulties" )
data <- rbind(rep(100,9) , rep(0,9) , x)


windows(20,14)
radarchart(data,plty=1,plwd=4,pcol=mypal,cglty=1,cglcol="grey60",axistype=1,axislabcol="grey50",
        caxislabels=c(0,25,50,75,100))

y9 <- tapply(baseline$Systemictherapysideeffects, baseline$Arm,mean,na.rm=T)
y10 <- tapply(baseline$Breast.symptoms, baseline$Arm,mean,na.rm=T)
y11 <- tapply(baseline$Arm.symptoms, baseline$Arm,mean,na.rm=T)
y12 <- tapply(baseline$Upset.by.hair.loss, baseline$Arm,mean,na.rm=T)


x<- as.data.frame(matrix( c(y9,y10,y11,y12) , ncol=4))
colnames(x) <- c("Systemic therapy side effects" , "Breast symptoms" ,
              "Arm symptoms","Upset by hair loss" )
data <- rbind(rep(100,4) , rep(0,4) , x)


windows(20,14)
radarchart(data,plty=1,plwd=4,pcol=mypal,cglty=1,cglcol="grey60",axistype=1,axislabcol="grey50",
        caxislabels=c(0,25,50,75,100))

########################################
##### 5.3 Follow-up evaluations
########################################

qol_global <- subset(qol, select=c(ID.patient,Arm,Day.of.visit,Visita,dif,Global.health.status, global_change,pain_new,physical_f ,role_f,
                        emotional_f,cognitive_f,social_f,fatigue_new,nausea_new,dyspnoea_new
,insomnia_new,appetite_new,future_function,arm_symptom,
```

```
                systematic_side,constipation_new,diarrhoea_new,financial_new,body
,sexual_function,sexual_enjoyment,breast_simp,hair_new,
                X29.Howwouldyourateyouroverallhealthduringthepastweek,
X30.Howwouldyourateyouroverallqualityoflifeduringthepastweek,
                X1.Doyouhaveanytroubledoingstrenuousactivities.likecarryingaheavyshoppingbagorasuitcase.,
X2.Do.you.have.any.trouble.taking.a.long.walk,
                X3.Doyouhaveanytroubletakingashortwalkoutsideofthehouse,
X4.Do.you.need.to.stayin.bed.or.a.chair.during.the.day,X5.Do.you.need.help.with.eating..dressing..washing.yourself.or.using.the.toilet.
                ))

qol_pacli <- subset(qol_global, Arm=="AC+pacli")
qol_ribo <- subset(qol_global, Arm=="Letro+Ribo")
qol_pacli2 <- subset(qol_global, Arm=="AC+pacli" & Visita=="0.Week1",select = c("ID.patient","Global.health.status"))
qol_pacli3 <- subset(qol_global, Arm=="AC+pacli" & Visita=="Pre-surgery", select = c("ID.patient","Global.health.status"))

dd <-merge(x = qol_pacli3, y = qol_pacli2, by = "ID.patient", all.x = TRUE)
dif <-as.numeric(dd$Global.health.status.x-dd$Global.health.status.y)

qol_pacli2 <- subset(qol_global, Arm=="Letro+Ribo" & Visita=="0.Week1",select = c("ID.patient","Global.health.status"))
qol_pacli3 <- subset(qol_global, Arm=="Letro+Ribo" & Visita=="Pre-surgery", select = c("ID.patient","Global.health.status"))

dd <-merge(x = qol_pacli3, y = qol_pacli2, by = "ID.patient", all.x = TRUE)
dif <-as.numeric(dd$Global.health.status.x-dd$Global.health.status.y)


#########################################################
#### 5.3 All plot for follow-up evaluations
#########################################################

### Global (0-100)
ribo_mean <- tapply(qol_ribo$global_change, qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$global_change, qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$global_change, qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$global_change, qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$global_change, qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$global_change, qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$global_change, qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$global_change, qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
          pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
          pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
          pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
          pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
          pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
```

```
      " "," "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")



##############################################
### 5.4: Analysis of global health status
##############################################

#install.packages("PROreg")
#library(PROreg)
library(lmerTest)
source("C:/Users/gvillacampa/Dropbox/VHIO/TFM/Code/BBmm.R")
source("C:/Users/gvillacampa/Dropbox/VHIO/TFM/Code/BBmm_EffectsEst_NR.R")
source("C:/Users/gvillacampa/Dropbox/VHIO/TFM/Code/BBmm_VarEst.R")
library(scales)
library(numDeriv)
library(rootSolve)


tfm <- subset(qol_global,Visita!="z_EoS")
tfm$dif2 <- tfm$dif/24  # Re-escalation of time

tfm$global_ordinal <- ifelse(tfm$X29.Howwouldyourateyouroverallhealthduringthepastweek==8,NA,
                             tfm$X29.Howwouldyourateyouroverallhealthduringthepastweek) +
 ifelse(tfm$X30.Howwouldyourateyouroverallqualityoflifeduringthepastweek==8,NA,
       tfm$X30.Howwouldyourateyouroverallqualityoflifeduringthepastweek)

names(tfm)[names(tfm)=="X1.Doyouhaveanytroubledoingstrenuousactivities.likecarryingaheavyshoppingbagorasuitcase."] <- "x1"
names(tfm)[names(tfm)=="X2.Do.you.have.any.trouble.taking.a.long.walk"] <- "x2"
names(tfm)[names(tfm)=="X3.Doyouhaveanytroubletakingashortwalkoutsideofthehouse"] <- "x3"
names(tfm)[names(tfm)=="X4.Do.you.need.to.stayin.bed.or.a.chair.during.the.day"] <- "x4"
names(tfm)[names(tfm)=="X5.Do.you.need.help.with.eating..dressing..washing.yourself.or.using.the.toilet."] <- "x5"

tfm$phyco_ordinal <- as.numeric(
 ifelse(tfm$x1==5, NA, tfm$x1)+
   ifelse(tfm$x2==5, NA, tfm$x2)+
   ifelse(tfm$x3==5, NA, tfm$x3)+
   ifelse(tfm$x4==5, NA, tfm$x4)+
   ifelse(tfm$x5==5, NA, tfm$x5)-5)

sum(is.na(  ifelse(tfm$x1==5, NA, tfm$x1)))
tfm <- subset(tfm, !is.na(global_ordinal))


##################################
#### Linear model estimation
##################################
mod4 <-lm( global_change ~ dif2*Arm , data = tfm); summary(mod4)

##################################
####  Tobit regression
##################################
library(VGAM)
summary(m <- vglm(global_change ~ dif2*Arm, tobit( Lower = -100, Upper = 100), data =tfm))
```

```
##################################
#### Linear mixed model
##################################
mod4 <-lmer( global_change ~  dif2*Arm+ (dif2| ID.patient), data =tfm); summary(mod4)
m <-  summary(mod4)
coef(mod4)
coef2 <- m$coefficients[,1]


##################################
#### PLot fitting binomial and beta-binomial
##################################
max <- 14
tfm$score <- tfm$global_ordinal
windows(20,14)
hist(tfm$score,breaks=seq(-0.5,max( tfm$score,na.rm=T)+0.5,1),col="grey80",ylab=" Score",las="1", main="Histogram ordinal
score",cex.main=1.5)

est <- BBest(tfm$score,max) # Parameter estimation
est.bi <- BIest(tfm$score,max) # Parameter estimation
lines(0:15, dim(tfm)[1]*dBB(15, est$p,est$phi),lwd=3, col="darkblue")
lines(0:15, dim(tfm)[1]*dBI(15, est$p),lwd=3, col="darkorange")


##################################
#### Generalised linear mixed model
##################################

library(scales)
z_intercept <- model.matrix(~tfm$ID.patient-1)
z_slope <- model.matrix(~tfm$ID.patient:tfm$dif2-1)
z_final <- cbind(z_intercept,z_slope)
## Generalized linear mixed model

model3<-glmer(cbind(score,max-score)~dif2*Arm+(dif2|ID.patient), family=binomial,data=tfm); summary(model3)

##################################
#### Beta-binomial mixed model
##################################

model <- BBmm(fixed.formula = score~dif2*Arm,Z=z_final,nRandComp =
c(nlevels(tfm$ID.patient),nlevels(tfm2$ID.patient)),m=max,data=tfm,show=TRUE)
summary(model)
coef <- model$fixed.coef

x <- seq(0,1,0.1)
plot(x,coef[1]+coef[2]*x+coef[3]+coef[4]*x,type="l",col="#00AFBB",ylim=c(-1.5,3.8),lwd=7)
lines(x,coef[1]+coef[2]*x,type="l",col="#E7B800",lwd=7)
for (i in 1:nlevels(tfm$ID.patient)){
 if (clean$Arm[i]=="Letro+Ribo"){
  lines(x,coef[1]+coef[2]*x+coef2[3]+coef[4]+model$random.coef[i]+model$random.coef[nlevels(tfm$ID.patient)+i]*x,
       type="l",col="#00AFBB",lty=2,lwd=0.5)
 } else{
  lines(x,coef[1]+coef[2]*x+model$random.coef[i]+model$random.coef[nlevels(tfm$ID.patient)+i]*x,
       type="l",col="#E7B800",lty=2,lwd=0.5)
 }
}

#  Beta-binomial mixed model (Only random intercept)
model2 <- BBmm(fixed.formula = score~dif2*Arm,random.formula = ~ID.patient,m=max,data=tfm)
summary(model2)

max-reg_global$global_ordinal
coef2 <- model2$fixed.coef

x <- seq(0,1,0.1)
```

```
plot(x,coef2[1]+coef2[2]*x+coef2[3]+coef2[4]*x,type="l",col="#00AFBB",ylim=c(-1.5,3.4),lwd=7)
lines(x,coef2[1]+coef2[2]*x,type="l",col="#E7B800",lwd=7)
for (i in 1:nlevels(tfm$ID.patient)){
 if (tfm$Arm[i]=="Letro+Ribo"){
  lines(x,coef2[1]+coef2[2]*x+coef2[3]+coef2[4]*x+model2$random.coef[i],
       type="l",col="#00AFBB",lty=2,lwd=0.5)
 } else{
  lines(x,coef2[1]+coef2[2]*x+model2$random.coef[i],
       type="l",col="#E7B800",lty=2,lwd=0.5)
 }
}

max <- 15
tfm$score <- tfm$phyco_ordinal
tfm2 <- subset(tfm, !is.na(phyco_ordinal))
windows(20,14)
hist(tfm2$score,breaks=seq(-0.5,max( tfm2$score,na.rm=T)+0.5,1),col="grey80",ylab=" Score",las="1", main="Histogram ordinal
score",cex.main=1.5)

est <- BBest(tfm2$score,max) # Parameter estimation
est.bi <- BIest(tfm2$score,max) # Parameter estimation
lines(0:15, dim(tfm2)[1]*dBB(15, est$p,est$phi),lwd=3, col="darkblue")
lines(0:15, dim(tfm2)[1]*dBI(15, est$p),lwd=3, col="darkorange")

## Longitudinal model
library(scales)
z_intercept <- model.matrix(~tfm2$ID.patient-1)
z_slope <- model.matrix(~tfm2$ID.patient:tfm2$dif2-1)
z_final <- cbind(z_intercept,z_slope)
## Generalized linear mixed model

model3<-glmer(cbind(score,max-score)~dif2*Arm+(dif2|ID.patient), family=binomial,data=tfm2); summary(model3)


model <- BBmm(fixed.formula = score~dif2*Arm,Z=z_final,nRandComp =
c(nlevels(tfm2$ID.patient),nlevels(tfm2$ID.patient)),m=max,data=tfm2,show=TRUE)
summary(model)
coef <- model$fixed.coef

x <- seq(0,1,0.1)
plot(x,coef[1]+coef[2]*x+coef[3]+coef[4]*x,type="l",col="#00AFBB",ylim=c(-1.5,3.8),lwd=7)
lines(x,coef[1]+coef[2]*x,type="l",col="#E7B800",lwd=7)
for (i in 1:nlevels(tfm2$ID.patient)){
 if (clean$Arm[i]=="Letro+Ribo"){
  lines(x,coef[1]+coef[2]*x+coef2[3]+coef[4]+model$random.coef[i]+model$random.coef[nlevels(tfm2$ID.patient)+i]*x,
       type="l",col="#00AFBB",lty=2,lwd=0.5)
 } else{
  lines(x,coef[1]+coef[2]*x+model$random.coef[i]+model$random.coef[nlevels(tfm2$ID.patient)+i]*x,
       type="l",col="#E7B800",lty=2,lwd=0.5)
 }
}

# Only random intercept
model2 <- BBmm(fixed.formula = score~dif2*Arm,random.formula = ~ID.patient,m=max,data=tfm2)
summary(model2)

max-reg_global$global_ordinal
coef2 <- model2$fixed.coef

x <- seq(0,1,0.1)
plot(x,coef2[1]+coef2[2]*x+coef2[3]+coef2[4]*x,type="l",col="#00AFBB",ylim=c(-1.5,3.4),lwd=7)
lines(x,coef2[1]+coef2[2]*x,type="l",col="#E7B800",lwd=7)
for (i in 1:nlevels(tfm2$ID.patient)){
 if (tfm2$Arm[i]=="Letro+Ribo"){
  lines(x,coef2[1]+coef2[2]*x+coef2[3]+coef2[4]*x+model2$random.coef[i],
       type="l",col="#00AFBB",lty=2,lwd=0.5)
```

```
  } else{
    lines(x,coef2[1]+coef2[2]*x+model2$random.coef[i],
          type="l",col="#E7B800",lty=2,lwd=0.5)
  }
}


###################################
##### Survival analysis
###################################

dd <- data.frame(id=unique(tfm$ID.patient[tfm$Visita=="0.Week1"]))
dd$time <- NA
dd$status <- NA
dd$treat <-  tfm$Arm[tfm$Visita=="0.Week1"]

i <- "1001-001"
for (i in unique(tfm$ID.patient)){
 j <-1
 final <- 0
 dd$time[dd$id==i] <-0
 n <- length(tfm$global_change[tfm$ID.patient==i])
 while (j <= n & final==0){

   if (tfm$global_change[tfm$ID.patient==i][j]< (-10)){

     final <- 1
     dd$time[dd$id==i] <- tfm$dif[tfm$ID.patient==i][j]
   }
   j <- j+1
 }
 dd$time[dd$id==i] <- ifelse(final==0, tfm$dif[tfm$ID.patient==i][j-1],dd$time[dd$id==i])
 dd$status[dd$id==i] <- final

}

library(survminer)
mypal <-  c( "#E7B800","#00AFBB")
surv_os <-survfit(Surv(dd$time, dd$status)~dd$treat);surv_os
cox <- coxph(Surv(dd$time, dd$status)~dd$treat);summary(cox)
plot(resid(cox))

windows(20,14)
plot(cox.zph(cox),lwd=1,col="red",lty=2)

windows(20,14)
plot(surv)
ggsurvplot(surv_os , data = dd,
          title = " ",
          pval = F, pval.method = F,    # Add p-value &  method name
          palette = mypal,
          risk.table = T,               # Add No at risk table
          cumevents = F,                # Add cumulative No of events table
          tables.height = 0.15,             # Specify tables height
          tables.theme = theme_cleantable(),  # Clean theme for tables
          tables.y.text = F,
          conf.int = F, # Hide tables y axis text
          xlab= "Time (months)",
          ylab="Time to 10-points deterioration",
          pval.size=4.5,
          risk.table.title="N. at risk",
          risk.table.fontsize=5,
          font.y=c(22),
          font.tickslab=20,
          size=2,
          font.x=c(20),
```

```
        linetype=c(1,1),
        censor.size=6,
        legend=c(0.9,1.8),
        legend.title = "",          # Change legend titles
        legend.labs = c("CI"," "),  # Change legend labels
        font.legend=c(14,"bold"),
        break.time.by=3,
        xlim=c(0,24),surv.median.line="hv")


################################
### Missing data analysis:
################################

# No data imputation
mod1 <-summary(lmer( global_change ~  dif2*Arm+ (dif2| ID.patient), data =tfm)); mod1
mod1$coefficients[4,1]
mod1$coefficients[4,1] + 1.96*mod1$coefficients[4,2]
mod1$coefficients[4,1] - 1.96*mod1$coefficients[4,2]

# Only individual with all evaluations
table(dat$Visita)
surgery <- subset(tfm, Visita=="Pre-surgery")
tfm_only_completed  <- tfm[tfm$ID.patient %in%  unique(surgery$ID.patient),]

mod2 <-summary(lmer( global_change ~  dif2*Arm+ (dif2| ID.patient), data =tfm_only_completed)); mod2
mod2$coefficients[4,1]
mod2$coefficients[4,1] + 1.96*mod2$coefficients[4,2]
mod2$coefficients[4,1] - 1.96*mod2$coefficients[4,2]


# Other imputation methods can be found in Missing_data_code.R
#####################################################################
######## Information with other scales
#####################################################################

### Physical (0-100)
ribo_mean <- tapply(qol_ribo$physical_f, qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$physical_f, qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$physical_f, qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$physical_f, qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
         ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
         ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
        ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
        ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$physical_f, qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$physical_f, qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$physical_f, qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$physical_f, qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
          pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
          pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
          pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
          pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
          pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])
```

```
final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
        " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### Role (0-100)
ribo_mean <- tapply(qol_ribo$role_f, qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$role_f, qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$role_f, qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$role_f, qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$role_f, qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$role_f, qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$role_f, qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$role_f, qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
          pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
          pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
          pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
          pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
          pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
        " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
```

```
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### Emotional (0-100)
ribo_mean <- tapply(qol_ribo$emotional_f, qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$emotional_f, qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$emotional_f, qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$emotional_f, qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$emotional_f, qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$emotional_f, qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$emotional_f, qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$emotional_f, qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
           pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
           pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
           pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
           pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
           pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
           pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
       " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### Cognitive (0-100)
ribo_mean <- tapply(qol_ribo$cognitive_f, qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$cognitive_f, qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$cognitive_f, qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$cognitive_f, qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])
```

```
final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$cognitive_f, qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$cognitive_f, qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$cognitive_f, qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$cognitive_f, qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
          pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
          pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
          pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
          pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
          pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
      " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### Social(0-100)
ribo_mean <- tapply(qol_ribo$social_f, qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$social_f, qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$social_f, qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$social_f, qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
         ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
         ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
        ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
        ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$social_f, qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$social_f, qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$social_f, qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$social_f, qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
          pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
          pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
          pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
```

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          pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
          pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
       " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### Body (0-100)
ribo_mean <- tapply(qol_ribo$body, qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$body, qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$body, qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$body, qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$body, qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$body, qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$body, qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$body, qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
          pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
          pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
          pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
          pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
          pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
       " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
```

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 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### Sexual functionin (0-100)
ribo_mean <- tapply(qol_ribo$sexual_function , qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$sexual_function , qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$sexual_function , qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$sexual_function , qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$sexual_function , qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$sexual_function , qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$sexual_function , qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$sexual_function , qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
          pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
          pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
          pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
          pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
          pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
      " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### Sexual enjoymnet (0-100)
ribo_mean <- tapply(qol_ribo$sexual_enjoyment , qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$sexual_enjoyment , qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$sexual_enjoyment , qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$sexual_enjoyment , qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
```

```
        ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
        ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$sexual_enjoyment , qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$sexual_enjoyment , qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$sexual_enjoyment , qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$sexual_enjoyment , qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
          pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
          pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
          pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
          pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
          pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
       " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### future_function (0-100)
ribo_mean <- tapply(qol_ribo$future_function, qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$future_function, qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$future_function, qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$future_function, qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$future_function, qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$future_function, qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$future_function, qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$future_function, qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
          pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
          pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])
```

```
pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
           pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
           pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
           pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
       " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### fatigue_new(0-100)
ribo_mean <- tapply(qol_ribo$fatigue_new, qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$fatigue_new, qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$fatigue_new, qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$fatigue_new, qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$fatigue_new, qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$fatigue_new, qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$fatigue_new, qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$fatigue_new, qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
           pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
           pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
           pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
           pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
           pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
           pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
       " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))
```

```
ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### Financial (0-100)
ribo_mean <- tapply(qol_ribo$financial_new , qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$financial_new , qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$financial_new , qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$financial_new , qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$financial_new , qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$financial_new , qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$financial_new , qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$financial_new , qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
           pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
           pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
           pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
           pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
           pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
           pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
       " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### diarrhoea_new (0-100)
ribo_mean <- tapply(qol_ribo$diarrhoea_new , qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$diarrhoea_new , qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$diarrhoea_new , qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$diarrhoea_new , qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])
```

```
ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$diarrhoea_new , qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$diarrhoea_new , qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$diarrhoea_new , qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$diarrhoea_new , qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
           pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
           pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
           pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
           pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
           pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
           pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
       " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### constipation_new(0-100)
ribo_mean <- tapply(qol_ribo$constipation_new, qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$constipation_new, qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$constipation_new, qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$constipation_new, qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
           ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
           ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$constipation_new, qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$constipation_new, qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$constipation_new, qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$constipation_new, qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
           pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
           pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
```

```
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
          pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
          pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
          pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
       " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")

###appetite_new (0-100)
ribo_mean <- tapply(qol_ribo$appetite_new , qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$appetite_new , qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$appetite_new , qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$appetite_new , qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$appetite_new , qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$appetite_new , qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$appetite_new , qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$appetite_new , qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
          pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
          pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
          pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
          pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
          pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
       " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))
```

```
ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,65)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### insomnia_new(0-100)
ribo_mean <- tapply(qol_ribo$insomnia_new, qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$insomnia_new, qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$insomnia_new, qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$insomnia_new, qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$insomnia_new, qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$insomnia_new, qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$insomnia_new, qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$insomnia_new, qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
          pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
          pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
          pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
          pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
          pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
      " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### dyspnoea_new(0-100)
ribo_mean <- tapply(qol_ribo$dyspnoea_new, qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$dyspnoea_new, qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$dyspnoea_new, qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$dyspnoea_new, qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
```

```
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
          ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
          ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$dyspnoea_new, qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$dyspnoea_new, qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$dyspnoea_new, qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$dyspnoea_new, qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
           pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
           pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
           pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
           pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
           pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
           pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
       " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")

### pain_new  (0-100)
ribo_mean <- tapply(qol_ribo$pain_new , qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$pain_new , qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$pain_new , qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$pain_new , qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
          ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
          ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$pain_new , qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$pain_new , qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$pain_new , qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$pain_new , qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
           pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
           pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
```

```
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
          pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
          pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
          pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
       " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### Global (0-100)
ribo_mean <- tapply(qol_ribo$nausea_new, qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$nausea_new, qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$nausea_new, qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$nausea_new, qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$nausea_new, qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$nausea_new, qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$nausea_new, qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$nausea_new, qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
          pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
          pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
          pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
          pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
          pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
       " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
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 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### breast_simp 0-100)
ribo_mean <- tapply(qol_ribo$breast_simp, qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$breast_simp, qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$breast_simp, qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$breast_simp, qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$breast_simp, qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$breast_simp, qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$breast_simp, qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$breast_simp, qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
          pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
          pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
          pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
          pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
          pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
      " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### hair_new(0-100)
ribo_mean <- tapply(qol_ribo$hair_new, qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$hair_new, qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$hair_new, qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$hair_new, qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
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          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$hair_new, qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$hair_new, qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$hair_new, qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$hair_new, qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
          pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
          pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
          pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
          pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
          pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
       " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")


### Systemictherapysideeffects(0-100)
ribo_mean <- tapply(qol_ribo$Systemictherapysideeffects, qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$Systemictherapysideeffects, qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$Systemictherapysideeffects, qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$Systemictherapysideeffects, qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$Systemictherapysideeffects, qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$Systemictherapysideeffects, qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$Systemictherapysideeffects, qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$Systemictherapysideeffects, qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
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          pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
          pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
          pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
          pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
          pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
       " "," "," ","EoS")
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")

dat$arm_symptom
### arm_symptom(0-100)
ribo_mean <- tapply(qol_ribo$arm_symptom, qol_ribo$Visita,mean,na.rm=T)
ribo_sd <- tapply(qol_ribo$arm_symptom, qol_ribo$Visita,sd,na.rm=T)
ribo_median <- tapply(qol_ribo$arm_symptom, qol_ribo$Visita,median,na.rm=T)
ribo_complet <- tapply(qol_ribo$arm_symptom, qol_ribo$Visita,summary,na.rm=T)
ribo_q1 <- c(ribo_complet$`0.Week1`[2],ribo_complet$`1.Week4`[2],ribo_complet$`2.Week8`[2],
          ribo_complet$`3.Week12`[2],ribo_complet$`4.Week16`[2],ribo_complet$`5.Week20`[2],
          ribo_complet$`Pre-surgery`[2],ribo_complet$z_EoS[2])

ribo_q3<- c(ribo_complet$`0.Week1`[5],ribo_complet$`1.Week4`[5],ribo_complet$`2.Week8`[5],
         ribo_complet$`3.Week12`[5],ribo_complet$`4.Week16`[5],ribo_complet$`5.Week20`[5],
         ribo_complet$`Pre-surgery`[5],ribo_complet$z_EoS[5])

final_ribo <- data.frame(group="ribo",time=
names(table(qol_ribo$Visita)),mean=ribo_mean,sd=ribo_sd,median=ribo_median,q1=ribo_q1,q3=ribo_q3 )

pacli_mean <- tapply(qol_pacli$arm_symptom, qol_pacli$Visita,mean,na.rm=T)
pacli_sd <- tapply(qol_pacli$arm_symptom, qol_pacli$Visita,sd,na.rm=T)
pacli_median <- tapply(qol_pacli$arm_symptom, qol_pacli$Visita,median,na.rm=T)
pacli_complet <- tapply(qol_pacli$arm_symptom, qol_pacli$Visita,summary,na.rm=T)

pacli_q1 <- c(pacli_complet$`0.Week1`[2],pacli_complet$`1.Week3`[2],pacli_complet$`2.Week6`[2],
          pacli_complet$`3.Week9`[2],pacli_complet$`4.Week12`[2],pacli_complet$`5.Week15`[2],
          pacli_complet$`6.Week18`[2],pacli_complet$`7.Week21`[2],
          pacli_complet$`Pre-surgery`[2],pacli_complet$z_EoS[2])

pacli_q3 <- c(pacli_complet$`0.Week1`[5],pacli_complet$`1.Week3`[5],pacli_complet$`2.Week6`[5],
          pacli_complet$`3.Week9`[5],pacli_complet$`4.Week12`[5],pacli_complet$`5.Week15`[5],
          pacli_complet$`6.Week18`[5],pacli_complet$`7.Week21`[5],
          pacli_complet$`Pre-surgery`[5],pacli_complet$z_EoS[5])

final_pacli <- data.frame(group="pacli",time=
names(table(qol_pacli$Visita)),mean=pacli_mean,sd=pacli_sd,median=pacli_median,q1=pacli_q1,q3=pacli_q3 )

final <-rbind(final_ribo, final_pacli)
final$t <- c(0,4,8,11.9,16,20,23.9,27.9,0.1,3,6,9,12.1,15,18,21,24.1,28)
lab <- c("","","3w","4w"," ","6w"," ","8w","9w"," ","","12w"," "," ","15w","16w"," ","18w"," ","20w","21w"," "," ","Pre-surgery (24w)",
       " "," "," ","EoS")
```

```
windows(20,12)
ggplot(final, aes(x=t, y=mean, group=group, color=group)) +
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd))

ggplot(final, aes(x=t, y=mean, group=group, color=group)) + xlim(lab)+
 geom_line()+ylim(-60,60)+ scale_color_manual(labels = c("Letro+Ribo", "AC+pacli"),values = c("#00AFBB", "#E7B800"))+
 geom_pointrange(aes(ymin=mean-sd, ymax=mean+sd),size=0.9) +theme_bw()+
 guides(color=guide_legend("Treatment"))+
 geom_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.7)+
 xlab("Time from study inclusion")+ylab("Change from baseline")

#############################################################################################################
## Linear mixed model
tfm$Arm2 <- tfm$Arm
tfm$Arm2 <- as.character(paste(tfm$Arm2))
tfm$Arm2[tfm$Arm2=="Letro+Ribo"]  <- "0.Letro+Ribo"
tfm$Arm2 <- as.factor(tfm$Arm2)

## GLobal
mod1 <-summary(lmer( global_change ~  dif2*Arm+ (dif2| ID.patient), data =tfm)); mod1
mod1$coefficients[2,1]
mod1$coefficients[2,1] + 1.96*mod1$coefficients[2,2]
mod1$coefficients[2,1] - 1.96*mod1$coefficients[2,2]

mod2 <-summary(lmer( global_change ~  dif2*Arm2+ (dif2| ID.patient), data =tfm));mod2
mod2$coefficients[2,1]
mod2$coefficients[2,1] + 1.96*mod2$coefficients[2,2]
mod2$coefficients[2,1] - 1.96*mod2$coefficients[2,2]

mod2$coefficients[4,1]
mod2$coefficients[4,1] + 1.96*mod2$coefficients[4,2]
mod2$coefficients[4,1] - 1.96*mod2$coefficients[4,2]


dat$global_change <- NA
dat$pain_new <- NA
dat$physical_f <- NA
dat$role_f <- NA
dat$emotional_f <- NA
dat$cognitive_f <- NA
dat$social_f <- NA
dat$fatigue_new <- NA
dat$nausea_new <- NA
dat$dyspnoea_new <- NA
dat$insomnia_new <- NA
dat$appetite_new <- NA
dat$constipation_new <- NA
dat$diarrhoea_new <- NA
dat$financial_new <- NA
dat$body <- NA
dat$sexual_function <- NA
dat$sexual_enjoyment <- NA
dat$breast_simp <- NA
dat$hair_new <- NA
dat$future_function <- NA
dat$systematic_side <- NA
dat$arm_symptom <- NA


## fatigue
mod1 <-summary(lmer( fatigue_new ~  dif2*Arm+ (dif2| ID.patient), data =tfm)); mod1
mod1$coefficients[2,1]
mod1$coefficients[2,1] + 1.96*mod1$coefficients[2,2]
mod1$coefficients[2,1] - 1.96*mod1$coefficients[2,2]

mod2 <-summary(lmer( fatigue_new ~  dif2*Arm2+ (dif2| ID.patient), data =tfm));mod2
```

```
mod2$coefficients[2,1]
mod2$coefficients[2,1] + 1.96*mod2$coefficients[2,2]
mod2$coefficients[2,1] - 1.96*mod2$coefficients[2,2]

mod2$coefficients[4,1]
mod2$coefficients[4,1] + 1.96*mod2$coefficients[4,2]
mod2$coefficients[4,1] - 1.96*mod2$coefficients[4,2]


## Financial
mod1 <-summary(lmer( financial_new ~  dif2*Arm+ (dif2| ID.patient), data =tfm)); mod1
mod1$coefficients[2,1]
mod1$coefficients[2,1] + 1.96*mod1$coefficients[2,2]
mod1$coefficients[2,1] - 1.96*mod1$coefficients[2,2]

mod2 <-summary(lmer( financial_new ~  dif2*Arm2+ (dif2| ID.patient), data =tfm));mod2
mod2$coefficients[2,1]
mod2$coefficients[2,1] + 1.96*mod2$coefficients[2,2]
mod2$coefficients[2,1] - 1.96*mod2$coefficients[2,2]

mod2$coefficients[4,1]
mod2$coefficients[4,1] + 1.96*mod2$coefficients[4,2]
mod2$coefficients[4,1] - 1.96*mod2$coefficients[4,2]

## diarrhoea
mod1 <-summary(lmer( diarrhoea_new ~  dif2*Arm+ (dif2| ID.patient), data =tfm)); mod1
mod1$coefficients[2,1]
mod1$coefficients[2,1] + 1.96*mod1$coefficients[2,2]
mod1$coefficients[2,1] - 1.96*mod1$coefficients[2,2]

mod2 <-summary(lmer( diarrhoea_new ~  dif2*Arm2+ (dif2| ID.patient), data =tfm));mod2
mod2$coefficients[2,1]
mod2$coefficients[2,1] + 1.96*mod2$coefficients[2,2]
mod2$coefficients[2,1] - 1.96*mod2$coefficients[2,2]

mod2$coefficients[4,1]
mod2$coefficients[4,1] + 1.96*mod2$coefficients[4,2]
mod2$coefficients[4,1] - 1.96*mod2$coefficients[4,2]

## constipation_new
mod1 <-summary(lmer( constipation_new ~  dif2*Arm+ (dif2| ID.patient), data =tfm)); mod1
mod1$coefficients[2,1]
mod1$coefficients[2,1] + 1.96*mod1$coefficients[2,2]
mod1$coefficients[2,1] - 1.96*mod1$coefficients[2,2]

mod2 <-summary(lmer( constipation_new ~  dif2*Arm2+ (dif2| ID.patient), data =tfm));mod2
mod2$coefficients[2,1]
mod2$coefficients[2,1] + 1.96*mod2$coefficients[2,2]
mod2$coefficients[2,1] - 1.96*mod2$coefficients[2,2]

mod2$coefficients[4,1]
mod2$coefficients[4,1] + 1.96*mod2$coefficients[4,2]
mod2$coefficients[4,1] - 1.96*mod2$coefficients[4,2]


## appetite
mod1 <-summary(lmer( appetite_new  ~  dif2*Arm+ (dif2| ID.patient), data =tfm)); mod1
mod1$coefficients[2,1]
mod1$coefficients[2,1] + 1.96*mod1$coefficients[2,2]
mod1$coefficients[2,1] - 1.96*mod1$coefficients[2,2]

mod2 <-summary(lmer( appetite_new  ~  dif2*Arm2+ (dif2| ID.patient), data =tfm));mod2
mod2$coefficients[2,1]
mod2$coefficients[2,1] + 1.96*mod2$coefficients[2,2]
mod2$coefficients[2,1] - 1.96*mod2$coefficients[2,2]
```

```
mod2$coefficients[4,1]
mod2$coefficients[4,1] + 1.96*mod2$coefficients[4,2]
mod2$coefficients[4,1] - 1.96*mod2$coefficients[4,2]

## insomnia
mod1 <-summary(lmer( insomnia_new  ~  dif2*Arm+ (dif2| ID.patient), data =tfm)); mod1
mod1$coefficients[2,1]
mod1$coefficients[2,1] + 1.96*mod1$coefficients[2,2]
mod1$coefficients[2,1] - 1.96*mod1$coefficients[2,2]

mod2 <-summary(lmer( insomnia_new  ~  dif2*Arm2+ (dif2| ID.patient), data =tfm));mod2
mod2$coefficients[2,1]
mod2$coefficients[2,1] + 1.96*mod2$coefficients[2,2]
mod2$coefficients[2,1] - 1.96*mod2$coefficients[2,2]

mod2$coefficients[4,1]
mod2$coefficients[4,1] + 1.96*mod2$coefficients[4,2]
mod2$coefficients[4,1] - 1.96*mod2$coefficients[4,2]


## dyspnoea_new
mod1 <-summary(lmer( dyspnoea_new ~  dif2*Arm+ (dif2| ID.patient), data =tfm)); mod1
mod1$coefficients[2,1]
mod1$coefficients[2,1] + 1.96*mod1$coefficients[2,2]
mod1$coefficients[2,1] - 1.96*mod1$coefficients[2,2]

mod2 <-summary(lmer( dyspnoea_new ~  dif2*Arm2+ (dif2| ID.patient), data =tfm));mod2
mod2$coefficients[2,1]
mod2$coefficients[2,1] + 1.96*mod2$coefficients[2,2]
mod2$coefficients[2,1] - 1.96*mod2$coefficients[2,2]

mod2$coefficients[4,1]
mod2$coefficients[4,1] + 1.96*mod2$coefficients[4,2]
mod2$coefficients[4,1] - 1.96*mod2$coefficients[4,2]
## pain_new
mod1 <-summary(lmer( pain_new ~  dif2*Arm+ (dif2| ID.patient), data =tfm)); mod1
mod1$coefficients[2,1]
mod1$coefficients[2,1] + 1.96*mod1$coefficients[2,2]
mod1$coefficients[2,1] - 1.96*mod1$coefficients[2,2]

mod2 <-summary(lmer( pain_new ~  dif2*Arm2+ (dif2| ID.patient), data =tfm));mod2
mod2$coefficients[2,1]
mod2$coefficients[2,1] + 1.96*mod2$coefficients[2,2]
mod2$coefficients[2,1] - 1.96*mod2$coefficients[2,2]

mod2$coefficients[4,1]
mod2$coefficients[4,1] + 1.96*mod2$coefficients[4,2]
mod2$coefficients[4,1] - 1.96*mod2$coefficients[4,2]

## nausea_new
mod1 <-summary(lmer( nausea_new  ~  dif2*Arm+ (dif2| ID.patient), data =tfm)); mod1
mod1$coefficients[2,1]
mod1$coefficients[2,1] + 1.96*mod1$coefficients[2,2]
mod1$coefficients[2,1] - 1.96*mod1$coefficients[2,2]

mod2 <-summary(lmer( nausea_new  ~  dif2*Arm2+ (dif2| ID.patient), data =tfm));mod2
mod2$coefficients[2,1]
mod2$coefficients[2,1] + 1.96*mod2$coefficients[2,2]
mod2$coefficients[2,1] - 1.96*mod2$coefficients[2,2]

mod2$coefficients[4,1]
mod2$coefficients[4,1] + 1.96*mod2$coefficients[4,2]
mod2$coefficients[4,1] - 1.96*mod2$coefficients[4,2]

## systematic_side
mod1 <-summary(lmer( systematic_side ~  dif2*Arm+ (dif2| ID.patient), data =tfm)); mod1
```

```
mod1$coefficients[2,1]
mod1$coefficients[2,1] + 1.96*mod1$coefficients[2,2]
mod1$coefficients[2,1] - 1.96*mod1$coefficients[2,2]

mod2 <-summary(lmer( systematic_side ~  dif2*Arm2+ (dif2| ID.patient), data =tfm));mod2
mod2$coefficients[2,1]
mod2$coefficients[2,1] + 1.96*mod2$coefficients[2,2]
mod2$coefficients[2,1] - 1.96*mod2$coefficients[2,2]

mod2$coefficients[4,1]
mod2$coefficients[4,1] + 1.96*mod2$coefficients[4,2]
mod2$coefficients[4,1] - 1.96*mod2$coefficients[4,2]

## Hair
mod1 <-summary(lmer( hair_new ~  dif2*Arm+ (dif2| ID.patient), data =tfm)); mod1
mod1$coefficients[2,1]
mod1$coefficients[2,1] + 1.96*mod1$coefficients[2,2]
mod1$coefficients[2,1] - 1.96*mod1$coefficients[2,2]

mod2 <-summary(lmer( hair_new ~  dif2*Arm2+ (dif2| ID.patient), data =tfm));mod2
mod2$coefficients[2,1]
mod2$coefficients[2,1] + 1.96*mod2$coefficients[2,2]
mod2$coefficients[2,1] - 1.96*mod2$coefficients[2,2]

mod2$coefficients[4,1]
mod2$coefficients[4,1] + 1.96*mod2$coefficients[4,2]
mod2$coefficients[4,1] - 1.96*mod2$coefficients[4,2]

##arm_symptom
mod1 <-summary(lmer( arm_symptom  ~  dif2*Arm+ (dif2| ID.patient), data =tfm)); mod1
mod1$coefficients[2,1]
mod1$coefficients[2,1] + 1.96*mod1$coefficients[2,2]
mod1$coefficients[2,1] - 1.96*mod1$coefficients[2,2]

mod2 <-summary(lmer( arm_symptom  ~  dif2*Arm2+ (dif2| ID.patient), data =tfm));mod2
mod2$coefficients[2,1]
mod2$coefficients[2,1] + 1.96*mod2$coefficients[2,2]
mod2$coefficients[2,1] - 1.96*mod2$coefficients[2,2]

mod2$coefficients[4,1]
mod2$coefficients[4,1] + 1.96*mod2$coefficients[4,2]
mod2$coefficients[4,1] - 1.96*mod2$coefficients[4,2]

## breast_simp
mod1 <-summary(lmer( breast_simp ~  dif2*Arm+ (dif2| ID.patient), data =tfm)); mod1
mod1$coefficients[2,1]
mod1$coefficients[2,1] + 1.96*mod1$coefficients[2,2]
mod1$coefficients[2,1] - 1.96*mod1$coefficients[2,2]

mod2 <-summary(lmer( breast_simp ~  dif2*Arm2+ (dif2| ID.patient), data =tfm));mod2
mod2$coefficients[2,1]
mod2$coefficients[2,1] + 1.96*mod2$coefficients[2,2]
mod2$coefficients[2,1] - 1.96*mod2$coefficients[2,2]

mod2$coefficients[4,1]
mod2$coefficients[4,1] + 1.96*mod2$coefficients[4,2]
mod2$coefficients[4,1] - 1.96*mod2$coefficients[4,2]


################################################
##### Pre-surgery evaluation:
################################################

baseline <- subset(dat, Visita=="Pre-surgery")
ribo <- subset(dat, c(Visita=="Pre-surgery",Arm=="Letro+Ribo"))
ct <- subset(dat, c(Visita=="Pre-surgery",Arm=="AC+pacli"))
```

```
table(baseline$Global.health.status)

x1 <- tapply(baseline$Physical.functioning, baseline$Arm,mean,na.rm=T)
x2 <- tapply(baseline$Role.functioning, baseline$Arm,mean,na.rm=T)
x3 <- tapply(baseline$Emotional.functioning, baseline$Arm,mean,na.rm=T)
x4 <- tapply(baseline$Cognitive.functioning, baseline$Arm,mean,na.rm=T)
x5 <- tapply(baseline$Social.functioning, baseline$Arm,mean,na.rm=T)
x<- as.data.frame(matrix( c(x1,x2,x3,x4,x5) , ncol=5))
colnames(x) <- c("Physical" , "Role" , "Emotional " ,
            "Cognitive" , "Social " )
data <- rbind(rep(100,5) , rep(0,5) , x)

mypal <-  c( "#E7B800","#00AFBB")
windows(20,14)
radarchart(data,plty=1,plwd=4,pcol=mypal,cglty=1,cglcol="grey60",axistype=1,axislabcol="grey50",
       caxislabels=c(0,25,50,75,100))

x6 <- tapply(baseline$Body.image, baseline$Arm,mean,na.rm=T)
x7 <- tapply(baseline$Sexual.functioning, baseline$Arm,mean,na.rm=T)
x8 <- tapply(baseline$Sexual.enjoyment, baseline$Arm,mean,na.rm=T)
x9 <- tapply(baseline$Future.perspective, baseline$Arm,mean,na.rm=T)

x<- as.data.frame(matrix( c(x6,x7,x8,x9) , ncol=4))
colnames(x) <- c("Body image" , "Sexual functioning" , "Sexual enjoyment" ,
            "Future perspective")
data <- rbind(rep(100,4) , rep(0,4) , x)

windows(20,14)
radarchart(data,plty=1,plwd=4,pcol=mypal,cglty=1,cglcol="grey60",axistype=1,axislabcol="grey50",
       caxislabels=c(0,25,50,75,100))

## Symptom scales
y0 <- tapply(baseline$Fatigue, baseline$Arm,mean,na.rm=T)
y1 <- tapply(baseline$Nausea.and.vomiting, baseline$Arm,mean,na.rm=T)
y2 <- tapply(baseline$Pain, baseline$Arm,mean,na.rm=T)
y3 <- tapply(baseline$Dyspnoea, baseline$Arm,mean,na.rm=T)
y4 <- tapply(baseline$Insomnia, baseline$Arm,mean,na.rm=T)
y5 <- tapply(baseline$Appetite.loss, baseline$Arm,mean,na.rm=T)
y6 <- tapply(baseline$Constipation, baseline$Arm,mean,na.rm=T)
y7 <- tapply(baseline$Diarrhoea, baseline$Arm,mean,na.rm=T)
y8 <- tapply(baseline$Financial.difficulties, baseline$Arm,mean,na.rm=T)

x<- as.data.frame(matrix( c(y0,y1,y2,y3,y4,y5,y6,y7,y8) , ncol=9))
colnames(x) <- c("Fatigue" , "Nausea and vomiting" , "Pain" ,
            "Dyspnoea" , "Insomnia","Appetite loss" , "Constipation","Diarrhoea","Financial difficulties" )
data <- rbind(rep(100,9) , rep(0,9) , x)

windows(20,14)
radarchart(data,plty=1,plwd=4,pcol=mypal,cglty=1,cglcol="grey60",axistype=1,axislabcol="grey50",
       caxislabels=c(0,25,50,75,100))

names(tfm)
y9 <- tapply(baseline$Systemictherapysideeffects, baseline$Arm,mean,na.rm=T)
y10 <- tapply(baseline$Breast.symptoms, baseline$Arm,mean,na.rm=T)
y11 <- tapply(baseline$Arm.symptoms, baseline$Arm,mean,na.rm=T)
y12 <- tapply(baseline$Upset.by.hair.loss, baseline$Arm,mean,na.rm=T)

x<- as.data.frame(matrix( c(y9,y10,y11,y12) , ncol=4))
colnames(x) <- c("Systemic therapy side effects" , "Breast symptoms" ,
            "Arm symptoms","Upset by hair loss" )
data <- rbind(rep(100,4) , rep(0,4) , x)
windows(20,14)
radarchart(data,plty=1,plwd=4,pcol=mypal,cglty=1,cglcol="grey60",axistype=1,axislabcol="grey50",
       caxislabels=c(0,25,50,75,100))
```