Non-Interventional Study Protocol
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Treatment satisfaction comparison in rheumatoid arthritis patients
between tofacitinib citrate and adalimumab,
each used in rheumatoid arthritis treatment

Statistical Analysis Plan
(SAP)

Version: **1.0**

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ABBREVIATION	DEFINITION
EULAR	The European League Against Rheumatism
RA	Rheumatoid Arthritis
TNF	Tumor Necrosis Factor
DMARD	Disease modifying antirheumatic drug
MTX	Methotrexate
DAS	Disease Activity Score
CRP	C-reactive protein
PSM	Propensity Score Method
PS	Propensity Score
IPTW	Inverse Probability of Treatment Weighting
SMD	Standardized Mean Difference
TSQM	Treatment Satisfaction Questionnaire for Medication
QoL	Quality of Life
EQ-5D	EuroQoL-5Dimensions
EQ-VAS	EuroQoL-Visual Analogue Scale
PRO	Patient Reported Outcome

VERSION HISTORY

Version	Effective Date	Change Type (New, Revise, Admin)	Summary of Revisions
1.0	12-MAR-2020	New	Not Applicable

1 INTRODUCTION

This statistical analysis plan (SAP) is presented to report the statistical methods used and results obtained in the treatment satisfaction comparison in rheumatoid arthritis patients between tofacitinib citrate and adalimumab, each used in rheumatoid arthritis treatment. The purpose of this observational study is to report the comparison of treatment satisfaction and quality of life in patients with rheumatoid arthritis treated with tofacitinib citrate or adalimumab.

CCI [redacted] *When the contents of the rht protocol are referenced, it is identified in italics.*

The documents below were reviewed for preparation of the SAP.

- "Treatment satisfaction comparison in rheumatoid arthritis patients between tofacitinib citrate and adalimumab, each used in rheumatoid arthritis treatment" Protocol version 3.0
- "Treatment satisfaction comparison in rheumatoid arthritis patients between tofacitinib citrate and adalimumab, each used in rheumatoid arthritis treatment" Medical records version 3.0
- "Treatment satisfaction comparison in rheumatoid arthritis patients between tofacitinib citrate and adalimumab, each used in rheumatoid arthritis treatment" Patient questionnaires version 1.0

CCI [redacted]

The purpose of this SAP is to describe the plans outlined to complete the Statistical Analysis Report (SAR) for "Treatment satisfaction comparison in rheumatoid arthritis patients between tofacitinib citrate and adalimumab, each used in rheumatoid arthritis treatment." Statistical analyses confirmed in this SAP could be used in future manuscripts for academic publication of the study outcomes.

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that causes joint destruction and leads to loss of function, decreased quality of life [1], and ultimately death [2] from complications. It is characterized by an excessive increase in pro-inflammatory cytokines that causes abnormal inflammation [3]. Therefore, the American Arthritis Foundation has recommended early diagnosis and appropriate treatment

targeting maintenance of low disease activity or remission of RA, prevention or delay of joint damage, and recovery of physical abilities and improvement in the quality of life [4].

According to the 2016 Update of the European League Against Rheumatism (EULAR) recommendation, the basic principle of the RA treatment goal is to provide the best care for the patients, and that treatment should be discussed and agreed between the two parties [5]. Therefore, patient evaluation of the treatment is an important factor for its success.

Recently, the development of new treatments with various mechanisms and diagnosis criteria for early detection have allowed diagnosis and treatments in earlier stages of RA than previously possible [6]. However, it is a chronic condition that is still difficult to cure, and various complications [7-10] and decreased quality of life [1] can occur with insufficient treatment or a prolonged disease presence. Within 2 years of diagnosis, irreversible bone erosion has been observed in more than 50% of patients [7], and it was shown that patients with prolonged disease period have a high risk for widespread complications, such as cardiovascular conditions [8], infection [9], and malignant tumor [10].

According to the 2015 American College of Rheumatology Guideline, patients who have insufficient response to or who do not have tolerance to the conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) as the 1st line treatment are recommended to switch to biologic DMARDs (bDMARDs) or the small molecular target therapy JAK suppressor (tofacitinib citrate) to minimize disease activity or to expedite remission [11]. Most patients who receive csDMARDs suffer from a prolonged disease period, and it is important to assess quality of life and treatment satisfaction in this population.

bDMARDs are injectibles, and they have been reported to have low compliance [12] owing to invasive administrations and loss of therapeutic effects from immunogenic response [13, 14]. On the contrary, tofacitinib citrate, which has been developed recently and used as an antirheumatic drug, is reported to have similar efficacy [15] and safety [16-18] as those of the bDMARDs and has a higher patient preference owing to its oral route of administration [19].

In a comparison using a RCT, non-inferior effects [15] and safety [20] of tofacitinib citrate were shown when compared to commonly used the bDMARD adalimumab, and both agents showed a higher quality of life than the placebo [21]. However, most clinical treatment success reports compare bDMARDs [22-24], and there are few reports that compare JAK suppressors with bDMARDs and their effects on patient treatment satisfaction and quality of life.

Therefore, the purpose of this study is to compare the two most common clinically used antirheumatic agents, adalimumab and tofacitinib, in terms of treatment satisfaction and

quality of life among Korean patients to assess treatment success from patients' perspectives.

1.1 STUDY DESIGN

This is a non-interventional, multicenter, cross-sectional, observational study. Through review of medical records, the study will analyze the comparison of treatment satisfaction and quality of life in patients with rheumatoid arthritis who have been treated with tofacitinib citrate or adalimumab between 6 months to 2 years to understand treatments in a clinical environment. Patient questionnaires will be used as part of the patients' self-reporting of results

1.1.1 Study Population

Subjects in this study include patients with rheumatoid arthritis at the participating institutions who have satisfied the inclusion criteria. Inclusion and exclusion criteria are defined in the study protocol.

1.1.2 Sample Size

The purpose of this study is to compare treatment satisfaction and quality of life in patients with RA who are receiving adalimumab or tofacitinib citrate. It is essential to identify the minimum sample size required to obtain statistically significant differences between the two groups. The equation below was used to calculate the sample size in this study [31].

$$N = \frac{2\sigma^2}{(\mu_1 - \mu_2)^2}\left[z_{1-\alpha/2} + z_{1-\beta}\right]^2$$

- σ: *Standard deviation from the overall satisfaction pooled ≈ 14.58 (SD1: 16 [18], SD2: 13 [24])*

$$\sigma = \sqrt{(\sigma_1{}^2 + \sigma_2{}^2)/2}$$

- μ_1: *Average of the overall satisfaction measured (larger) = 83 [24]*
- μ_2: *Average of the overall satisfaction measured (smaller) = 79 [24]*
- $z_{1-\alpha/2}$: *95% confidence interval (double-sided) significance = 1.96*
- $z_{1-\beta}$: *80% power threshold = 0.842*

Sample size was calculated based on literature that compared the median general satisfaction number between two drugs from the TSQM and the EQ-5D index score [24].

Jobanputra P et al. (2010) reported that the median EQ-5D index score and the median overall satisfaction score from TSQM (interquartile range) at 3 months after taking the medication in the adalimumab group were 0.62 (0.59–0.76) and 83 (67–100), respectively. In contrast, these scores were 0.62 (0.52–0.76) and 79 (58–92), respectively, in the etanercept group. Based on the sample number calculated in this study, we assumed that the average scores for the EQ-5D index or TSQM would be similar to the median scores from this measurement tool. This is because the interquartile ranges were almost symmetrical to the median value. We also assumed that the difference between the 3rd interquartile and median values (or the difference between the median and the 1st interquartile values) would replace the deviation from the general EQ-5D index or TSQM scores. This is because approximately 67% of the normal distribution data falls within the average ± 1 standard deviation, whereas 50% of uniform distribution data falls within median ± interquartile (in other words, within the interquartile range: Q1–Q3) values. Based on these assumptions, the standard deviations for the EQ-5D index scores were from 0.03 (= 0.62–0.59) to 0.14 (= 0.76–0.62) in adalimumab and from 0.1 (= 0.62–0.52) to 0.14 (=0.76–0.62) in etanercept. Under the same assumption, the standard deviations for the TSQM scores were from 16 (= 83–67) to 17 (= 100–83) in adalimumab and from 13 (= 92–79) to 21 (= 79–58) in etanercept.

We assumed 0 (= 0.62–0.62) and 4 (= 83–79) points as the difference in the average EQ-5D and TSQM scores between patients receiving adalimumab and tofacitinib citrate. We also assumed the standard deviations as 0.03–0.14 and 16–17 points for the EQ-5D index and TSQM, respectively, in patients receiving adalimumab and in patients receiving tofacitinib citrate, the EQ-5D index and TSQM as 0.1–0.4 points and 13–21 points, respectively. Through various combinations of standard deviations, we assumed that the minimum pooled standard deviation is 0.07 (= $\sqrt{(0.03^2 + 0.1^2)/2}$ *and 14.58 (=* $\sqrt{(16^2 + 13^2)/2}$ *), and the maximum pooled standard deviation is 0.14 (=* $\sqrt{(0.14^2 + 0.14^2)/2}$*) and 19.1 (=* $\sqrt{(17^2 + 21^2)/2}$*) in the EQ-5D index and TSQM, respectively.*

It was calculated that a total of 32 subjects in each group will be needed to detect the average difference of 0.05 points in EQ-5D with an 80% power at 5% significance, and a standard deviation of 0.07. The average difference of EQ-5D between the groups from a previous study was 0, which could not be used to calculate the sample size. Therefore, we voluntarily selected a small number, 0.05, as the average difference for the calculation. If 0.14 is used as the pooled standard deviation, a total of 125 per group will be needed.

When 14.58 is set as the pooled standard deviation for TSQM, a total of 209 subjects will be needed for each group for an 80% power with 5% significance. If 19.1 is set as the pooled standard deviation, a total of 359 subjects will be needed for each group.

Based on the above calculations of the range of sample sizes for each group, the most number needed for each group, conservatively, is 360 subjects. Considering 10–20% of subjects not consenting, the actual sample size would be 400–450 subjects per group. Therefore, approximately 420 subjects will be identified from each group from the total of 840 subjects in this study.

Considering the geographic distribution and the number of patients as well as the clinical experiences and the academic success of the physicians, institutions participating in this study are deemed representative hospitals to care for patients with RA in Korea. Therefore, we believe that subjects who are screened from these institutions and undergo inclusion/exclusion criteria and the consent process are representative of Korea's patients with rheumatoid arthritis who either use tofacitinib citrate or adalimumab.

1.1.3 Data Source

Once a subject satisfies the inclusion criteria and voluntarily consents to participate in the study, subject data will be collected through review of medical records and patient questionnaires. Variables collected from the medical chart include demographic and clinical characteristics. Educational status, total income for the past year, and the current employment status will be collected from the questionnaires. Treatment satisfaction and the quality of life questions will be collected using the TSQM questionnaires and EQ-5D measurements, and the subject will self-record these.

1.2 STUDY OBJECTIVES

This study aim to compare treatment satisfaction and quality of life between patients who have been using tofacitinib citrate and patients who have been using adalimumab for 6 months or more and less than 2 year in treatment of rheumatoid arthritis.

1.2.1 Primary Objective

To compare the treatment satisfaction between tofacitinib citrate users and adalimumab users.

1.2.2 Secondary Objectives

To compare the quality of life between tofacitinib citrate users and adalimumab users

2 INTERIM ANALYSES

Not Applicable

3 HYPOTHESES AND DECISION RULES

3.1 STATISTICAL HYPOTHESES

This is a non-interventional, multicenter, cross-sectional study intended to evaluate treatment satisfaction and quality of life in patients with rheumatoid arthritis who are taking tofacitinib citrate or adalimumab between 6 months to 2 years. Therefore, there is no statistical hypothesis.

3.2 STATISTICAL DECISION RULES

- *If a statistical test is required, it should be carried out at the two-side significant level 5%.*
- *When multivariable analysis is performed, independent variables used for actual analysis can be added or subtracted considering the structure of collected data and general characteristics of study subjects.*
- *When the analysis with propensity score matching is performed, paired t-test, McNemar's test, Linear mixed model, conditional logistic regression, etc. are used for analysis.*

4 ANALYSIS SETS/POPULATIONS

4.1 FULL ANALYSIS SET

All subjects that have satisfied the inclusion criteria and were registered for the study. Inclusion and exclusion criteria are outlined in the study protocol section 7.2.

4.2 SAFETY ANALYSIS SET

Not Applicable

4.3 OTHER ANALYSIS SET

Not Applicable

4.4 SUBGROUPS

Not Applicable

5 ENDPOINTS AND COVARIATES

Endpoints and covariates evaluated in this study are as follows:

5.1 EFFICACY/EFFECTIVENESS ENDPOINT(S)

Variable	Role	Data source	Operational definition
Treatment satisfaction	Outcome	Patient questionnaire	▪ 14 questions applicable for treatment satisfaction measurement - Self-reporting questionnaire for evaluating treatment satisfaction - Four domains including effectiveness, convenience, global satisfaction, and side effects - Scores for each domain are calculated based on the equation - Range of 0–100 ▪ Higher numbers indicate higher treatment satisfaction
EQ-5D index	Outcome	Patient questionnaire	▪ Standardized tool for measuring overall health ▪ EQ-5D index: 15 questions for assessing quality of life - Five domains, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression - Scores for each domain are calculated based on the equation ▪ Higher scores indicate better health
EQ VAS	Outcome	Patient questionnaire	▪ Standardized tool for measuring overall health ▪ EQ VAS: Value for evaluating overall health - Range of 0–100 ▪ Higher scores indicate better health

5.2 SAFETY ENDPOINTS

Not Applicable

5.3 OTHER ENDPOINTS

Not Applicable

5.4 COVARIATES

Item	Variables	Role	Data source	Operational definition
Basic characteristics	Age	Covariate	Medical chart	▪ Used entered value
	Gender	Covariate	Medical chart	▪ Used entered value
Demographics	Educational level	Covariate	Patient questionnaire	▪ Used entered value
	Financial status	Covariate	Patient questionnaire	▪ Used entered value
	Employment status	Covariate	Patient questionnaire	▪ Used entered value
Clinical characteristics	Body mass index	Covariate	Medical chart	▪ Calculated as weight (kg) / height (m^2)
	Comorbidities	Covariate	Medical chart	▪ Used entered value
	Duration of rheumatoid arthritis	Covariate	Medical chart	Days between initial diagnosis and assessed date calculated
	Erythrocyte sedimentation rate	Covariate	Medical chart	▪ Used entered value
	C-reactive protein level	Covariate	Medical chart	▪ Used entered value
	Tender joint count	Covariate	Medical chart	▪ Used entered value
	Swollen joint count	Covariate	Medical chart	▪ Used entered value
	Pain VAS score	Covariate	Medical chart	▪ Used entered value
	Previously used drugs	Covariate	Medical chart	▪ Used entered value
	Currently used drugs	Covariate	Medical chart	▪ Used entered value

Item	Variables	Role	Data source	Operational definition
	Treatment numbers	Covariate	Medical chart	▪ Used entered value
	Treatment dose	Covariate	Medical chart	▪ Used entered value
	Treatment duration	Covariate	Medical chart	▪ Days between treatment initiation and assessed date
	Concomitant csDMARDs use	Covariate	Medical chart	▪ Used entered value
	Number of concomitant csDMARDs	Covariate	Medical chart	▪ Assessed the number of drugs recorded
	Type of concomitant csDMARDs	Covariate	Medical chart	▪ Used entered value
	Dose of concomitant csDMARDs	Covariate	Medical chart	▪ Used entered value
	Duration of concomitant csDMARDs use	Covariate	Medical chart	▪ Used entered value ▪ Days between initial treatment administration and assessed date
	Concomitant NSAIDs use	Covariate	Medical chart	▪ Used entered value
	Number of concomitant NSAIDs	Covariate	Medical chart	▪ Assessed the number of drugs recorded
	Type of concomitant NSAIDs	Covariate	Medical chart	▪ Used entered value
	Dose of concomitant NSAIDs	Covariate	Medical chart	▪ Used entered value
	Duration of concomitant NSAIDs use	Covariate	Medical chart	▪ Used entered value ▪ Days between initial treatment administration and assessed date
	Concomitant steroid use	Covariate	Medical chart	▪ Used entered value
	Number of concomitant steroids	Covariate	Medical chart	▪ Assessed the number of drugs recorded
	Type of concomitant	Covariate	Medical	▪ Used entered value

Item	Variables	Role	Data source	Operational definition
	steroid		chart	
	Dose of concomitant steroid	Covariate	Medical chart	▪ Used entered value
	Duration of concomitant steroid use	Covariate	Medical chart	▪ Used entered value ▪ Days between initial treatment administration and assessed date

6 HANDLING OF MISSING VALUES

In the case of data that do not have a bias in the interpretation of the results, the analysis is carried out based on only the observed data without adjusting the missing values. If it is deemed that significant bias is imposed on the interpretation of the results when the analysis is carried out with only the observed data, the analysis is carried out by statistically adjusting the missing values using the following appropriate missing value imputation method. As a method of replacing missing values, methods such as mean imputation, median imputation, probability imputation, regression imputation, ratio imputation, or multiple imputation are used depending on the pattern of missing values.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL METHODS

7.1.1 Analysis of Continuous Data

Continuous data will be presented as the average, standard deviation, median, and range (minimum and maximum). When normal distribution of data cannot be assumed, data will be presented as median, range, and interquartile range. When group comparison is needed, the Student's *t*-test or analysis of variance (ANOVA) will be used for continuous variables, as long as there is no deviance from the assumption of normality. If normality assumption is not satisfied, non-parametric methods, such as the Mann-Whitney's U test or Kruskal-Wallis test, will be used. In this case, histograms for each continuous variable will be used to evaluate normality assumption, and the parametric evaluation will be referenced for reviewing the result. However, if data involve analysis after propensity score matching, the paired *t*-test (or a non-parametric method such as the Wilcoxon signed-rank test) will be substituted to suit the characteristics of the matched data.

7.1.2 Analysis of Categorical Data

Categorical data will be calculated as frequency or percentage. When group comparison is needed, the chi-square test will be used for categorical variables; however, the Fisher's exact test, which is a non-parametric method, will be used if more than 20% of the expected cell frequency is less than 5%. However, if data involve analysis after propensity score matching, McNemar's test or the generalized McNemar's test will be substituted to suit the characteristics of the matched data.

7.1.3 Descriptive Analysis

Treatment satisfaction will be presented as average, standard deviation, median (interquartile range) and range (minimum, maximum) for each domain, and quality of life will be presented as average, standard deviation, median (interquartile range), and range (minimum, maximum) for the EQ-5D index and EQ VAS. Differences in patient demographic and clinical characteristic variables will be compared using the Student's *t*-test or ANOVA. If collected variables do not satisfy the assumptions needed for parametric validation, non-parametric methods such as the Mann-Whitney's U-test or Kruskal-Wallis test will be used for analysis. When patient characteristics are continuous, the Pearson's correlation analysis or Spearman's correlation analysis will be used to analyze the correlation with dependent variables. However, if data involve analysis by propensity score matching, analytical methods that suit this characteristic will be substituted.

7.1.4 Statistical Software

All statistical analyses will be performed using Windows SAS® version 9.4 (Cary, NC, USA)

7.2 STATISTICAL ANALYSES

7.2.1 Epidemiological Characteristics

Subject demographics and clinical characteristics will be presented in a table. Continuous data will be presented as the average, standard deviation, median, and range (minimum and maximum), and categorical data will be presented as frequency and percentage.

A. Demographics
   1. Age
   2. Gender
   3. Education level
   4. Financial status
   5. Current employment

B. Clinical characteristics
   1. Body mass index
   2. Co-morbidities
   3. Initial RA diagnosis date
   4. Previously used types of DMARDs
   5. Currently used DMARD (tofacitinib citrate or adalimumab), treatment numbers/duration/dose

6. Concurrently used drug types, numbers, and doses (csDMARDs/NSAIDs/steroid)
7. DAS28 components

7.2.2 Safety Analyses

Not Applicable

7.2.3 Analyses of Endpoints

7.2.3.1 Propensity Score Matching

There are concerns of selection bias in the selection of the subject population in observational studies, and there are limitations in inferring correlations owing to the absence of randomization. Selection bias means there is a higher chance of subjects being assigned to a treatment arm based on a particular covariate, and this covariate can be a disturbing variable in establishing the difference between the treatment groups [37]. In order to balance the covariates between the groups, the propensity score method can be used. For example, a study by Bangalore et al. (2015) involved patients with polyvascular disease, and in this study, 1:1 matching was performed through propensity scores using demographic and clinical characteristics as matching variables to compare the mortality rate and risk ratio between CAGB and PCI groups. Although there was no significant difference in mortality rate, the PCI group had a higher risk of myocardial infarction than the CAGB group [38].

In this study, the difference in treatment satisfaction and quality of life scores between the two groups that have been matched by propensity score will be compared. Propensity scores will be calculated using subjects' demographic and clinical characteristics as covariates. Matching will be done using the greedy matching (nearest neighbor) method. Assuming the ratio of 2:1, the greedy matching method will randomly select one subject from treatment group 2 and set a range of propensity scores using treatment group 2 as the center through the caliper. Two subjects from treatment group 1 that have the closest propensity scores will be selected. In this case, the caliper will be determined after reviewing the data. If more than 25% of the standard group is eliminated after matching or if the distribution of covariates in the two groups are thought to be different, inverse probability of treatment weighting (IPTW) can be used for analysis.

7.2.3.2 Treatment Satisfaction

Treatment domains (effectiveness, side effects, convenience, and global satisfaction) will be presented as the average, standard deviation, median (interquartile range), and range (minimum, maximum). Multivariate linear regression analysis will be used to evaluate treatment satisfaction based on the demographic and clinical characteristics that affect each domain of the treatment satisfaction. However, if data involve analysis after propensity score matching, a linear mixed model will be substituted to suit the characteristics of the matched data.

7.2.3.3 Quality of Life

The EQ-5D index and EQ VAS will be presented as an average, standard deviation, median (interquartile range), and range (minimum, maximum), and each domain of EQ-5D (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) will be presented as frequency. In order to evaluate the quality of life based on demographic and clinical characteristics that affect the computed EQ-5D index and EQ VAS, multivariate linear regression analysis will be used, and data transformation or quantile regression can be used after confirming data distribution. However, if data involve analysis after propensity score matching, analytical methods that suit the characteristics of the matched data will be substituted.

7.2.4 Summary of Analyses

Outcome	Analysis Set	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
Treatment satisfaction	FAS	*Not Applicable*	Multivariate linear regression analysis	Demographics and treatment pattern variables	After reviewing the data, substitute with the multiple imputation (MI) method. However, covariates that do not affect the results will not be

					substituted.
EQ-5D index	FAS	*Not Applicable*	Multivariate linear regression analysis	Demographics and treatment pattern variables	After reviewing the data, substitute with the MI method. However, covariates that do not affect the results will not be substituted.
EQ VAS	FAS	*Not Applicable*	Multivariate linear regression analysis	Demographics and treatment pattern variables	After reviewing the data, substitute with the MI method. However, covariates that do not affect the results will not be substituted.

8 DERIVED VARIABLES

Variable Name	Description	Valid Value	Computation Method, Notes, or Equation(s)
Duration of rheumatoid arthritis	Duration of disease	> 0.0	▪ Duration (year, month, day) between case assessed date and the date of initial diagnosis
Treatment duration	Treatment duration	> 0.0	▪ Duration (year, month, day) between case assessed date and the initiation date of drug currently being used
Treatment satisfaction questionnaire for medication (TSQM)	Treatment Satisfaction	0 to 100	▪ Classification of treatment satisfaction (14 questions) - effectiveness - convenience - global satisfaction - side effect ▪ Each domain will be defined if all items for the domain are present or if only one item is missing. If two or more items are missing, the affected domain will be invalid (treated as missing value). ▪ Effectiveness - ([(No. 1 + No. 2 + No. 3) - 3] / 18) × 100 - If one question is missing: ([Sum of {No. 1 + No. 2 + No. 3} - 2] / 12) × 100 ▪ Side-Effect - If No. 4 = No, score = 100 - If not, ([Sum of {No. 5 – No. 8} - 4] / 16) × 100 - If one question is missing: ([Sum of {No. 5 – No. 8} - 3] / 12) × 100 ▪ Convenience - ([Sum of No. 9 – No. 11} - 3] / 18) × 100 - If one question is missing: ([Sum of {No. 9 – No. 11} - 2] / 12) × 100 ▪ Global-Satisfaction - ([(No. 12 + No. 13+ No. 14) - 3] / 14) × 100 - If No. 12 or No 13 is missing: ([(No. 12 + No. 13+ No. 14) - 2] / 10) × 100 - If No. 14 is missing: ([(No. 12 + No. 13) - 2] / 8) × 100

<table>
<tr><th>Variable Name</th><th>Description</th><th>Valid Value</th><th>Computation Method, Notes, or Equation(s)</th></tr>
<tr><td>EuroQoL-5 Dimensions index, EQ-5D index</td><td>Quality of life</td><td></td><td>▪ Classification of quality of life (15 questions)
- mobility
- self-care
- usual activities
- (pain/discomfort
- anxiety/depression
▪ EQ-5D index
1 - (0.0081 + (0.1140 × M2 + 0.6274 × M3 + 0.0572 × SC2 + 0.2073 × SC3 + 0.0615 × UA2 + 0.2812 × UA3 + 0.0581 × PD2+ 0.2353 × PD3 + 0.0675 × AD2 + 0.2351 × AD3))

<table><tr><th>Variable Name</th><th>Definition</th></tr><tr><td>M2</td><td>If mobility is ‘level 2,’ then 1; if not, 0</td></tr><tr><td>M3</td><td>If mobility is ‘level 3,’ then 1; if not, 0</td></tr><tr><td>SC2</td><td>If self-care is ‘level 2,’ then 1; if not, 0</td></tr><tr><td>SC3</td><td>If self-care is ‘level 3,’ then 1; if not, 0</td></tr><tr><td>UA2</td><td>If usual activity is ‘level 2,’ then 1; if not, 0</td></tr><tr><td>UA3</td><td>If usual activity is ‘level 3,’ then 1; if not, 0</td></tr><tr><td>PD2</td><td>If pain/discomfort is ‘level 2,’ then 1; if not, 0</td></tr><tr><td>PD3</td><td>If pain/discomfort is ‘level 3,’ then 1; if not, 0</td></tr><tr><td>AD2</td><td>If anxiety/depression is ‘level 2,’ then 1; if not 0.</td></tr><tr><td>AD3</td><td>If anxiety/depression is ‘level 3,’ then 1; if not, 0</td></tr><tr><td>N3</td><td>If there is at least one ‘level 3,’ then 1; all others are 0</td></tr></table></td></tr>
</table>

Variable Name	Description	Valid Value	Computation Method, Notes, or Equation(s)
			Mobility level 1: no effects, level 2: sometimes affected, level 3: very affected. Self-care Level 1: no effects, level 2: sometimes affected, level 3: very affected. Usual activities level 1: no effects, level 2: sometimes affected, level 3: very affected. Pain/discomfort level 1: none, level 2: sometimes, level 3: often. Anxiety/Depression level 1: none, level 2: sometimes. level 3: often

9 LIST OF TABLES AND TABLE SHELLS

Supplements

10 REFERENCES

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