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**Maastricht University**

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**Faculty of Sciences**  
**School for Information Technology**

Master of Statistics

**Masterthesis**

***A randomized controlled study to compare efficacy of continuous versus pulsed radiofrequency treatment of genicular nerves to alleviate pain and functional impairment in patients with advanced osteoarthritis of the knee.***

**Fenny Ong**

Thesis presented in fulfillment of the requirements for the degree of Master of Statistics, specialization Biostatistics

**SUPERVISOR :**

Prof. dr. Tomasz BURZYKOWSKI

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Dr. Luc VANLINTHOUT

Transnational University Limburg is a unique collaboration of two universities in two countries: the University of Hasselt and Maastricht University.



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**2017**  
**2018**



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## Abstract

**Introduction:** Osteoarthritis is a chronic progressive disease which is a leading source of pain and disability among elderly population. No medication can reverse or stop the progression of this disease. Over the decades, the so-called continuous radiofrequency (CRF) has been added as an option for the management of different pain syndrome, including osteoarthritis. Along with the broadening of the application of CRF, a modified technique was developed and labelled as the pulsed radiofrequency (PRF). This new procedure aimed to achieve pain relief without creating permanent damage as seen in CRF.

**Objective:** The objective of this study is to compare the efficacy of CRF and PRF in alleviating pain and functional impairment in patients with advanced osteoarthritis, as evaluated using Visual Analogue Scale (VAS), Western Ontario and McMaster Universities (WOMAC) index of osteoarthritis, and 12-item short form health survey (SF-12).

**Methodology:** A full multivariate normal model with group-by-time interaction for the fixed effects and unstructured variance-covariance matrix was applied for the analysis of each outcome in this study. This likelihood-based analysis is considered valid under the assumption of missing data mechanism missing at random (MAR). Since the possibility of missing not at random (MNAR) cannot be ruled out, sensitivity analysis under the construction of pattern-mixture model with identifying restrictions strategy combined with the concept of multiple imputation was also conducted in the study.

**Results:** By taking the missingness in the data into account, the mean changes of VAS and WOMAC from baseline differ statistically significant for patients receiving CRF versus PRF treatment at each evaluation time-point (month 1, 6, and 12 after treatment). There is also statistically significant difference in the PCS outcome at month 6 and 12 after treatment. In general the patients receiving CRF showed better results compared to those receiving PRF. In contrast, patients in both groups did not show any significant difference for the outcome of MCS.

**Keywords:** Continuous radiofrequency, pulsed radiofrequency, missing at random, missing not at random, multivariate, pattern-mixture model, complete case missing values, neighboring case missing values, multiple imputation.

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I am indebted to PT DEXA Medica for the sponsorship and opportunity given to me in pursuing my higher academic level. It is my good luck to work in a place that gives support for the development of its employee.

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<sup>1</sup> Ogalla IR, Martín AM, Santana Pineda MM, Rodríguez Huertas F, Ogalla R, Martín M. Effectiveness of genicular nerve radiofrequency treatment in knee osteoarthritis chronic pain. *Rev Soc Esp Dolor*. 2014;21:212-8.

<sup>2</sup> Santana Pineda MM, Vanlinthout LE, Moreno Martín A, van Zundert J, Rodríguez Huertas F, Novalbos Ruiz JP. Analgesic effect and functional improvement caused by radiofrequency treatment of genicular nerves in patients with advanced osteoarthritis of the knee until 1 year following treatment. *Reg Anesth Pain Med*. 2017;42:62-8.

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# 1 Introduction

Osteoarthritis (OA) is a chronic progressive disease involving the thinning of cartilage in joints and a leading source of pain and disability among elderly population throughout the world. Nowadays an approximated 15% of adults over 60 years around the world have some degree of OA and it is predicted that by 2050 there will be 130 million people who will suffer from the disease. It is suggested that recent environmental changes have played a significant role in doubling the prevalence of OA since the mid-20th century. Because of its function-impairing nature, the burden of this disease on society, both in terms of its epidemiology and economic impact, is quite substantial [1,2].

Since there are no medicines that can reverse or stop the progression of the disease, the objectives of OA management are mainly to mitigate pain, reduce inflammation, slow cartilage degradation, improve function, reduce disability, and improve the quality of life. The treatment of OA consists of non-pharmacological treatment, pharmacological treatment, and surgery. The long-term efficacy of the pharmacological treatments is often variable or is yet to be determined. In addition, the trade-offs between the risks and benefits must be assessed because side effects are common [1]. While often being considered as the last source of intervention, the surgical management are still associated with increased morbidity and mortality. Moreover, although the procedure is successful at providing pain relief for many patients, there is a proportion of patients who experience a poor outcome after surgery [3].

Radiofrequency (RF) has been introduced for treating various chronic pain, which procedure is based on the theory that cutting the nerve responsible to a painful structure may alleviate pain and restore function [4]. The conventional or continuous radiofrequency (CRF) procedure increases the temperature sufficiently to create permanent damage to the nerve cells responsible for the pain impulses. Recently, the modified technique labelled the pulsed radiofrequency (PRF) was introduced. This procedure avoids thermal lesioning in order to achieve pain relief without creating permanent damage to the tissues [5]. Because of this non-destructive feature, PRF may mitigate concern regarding possible complications. Regardless of several studies comparing the efficacy of CRF versus PRF [6,7,8], there is a lack of study in osteoarthritis case, which underlay the current study.





## 2 Objective

The objective of this study is to compare the efficacy of CRF and PRF in alleviating pain and functional impairment in patients with advanced osteoarthritis. The pain was evaluated using a 0-10 Visual Analogue Scale (VAS) and the functional impairment was assessed using Western Ontario and McMaster Universities (WOMAC) index of osteoarthritis as well as 12-item short form health survey (SF-12). It is of interest to study whether the mean changes of the pain and functional impairment from baseline differ for patients receiving CRF versus PRF treatment, by taking into consideration the missingness in the data.



### 3 Data

The data used in this study are from a randomized and controlled clinical trial in patients with grade 3-4 gonarthrosis suffering from intractable knee pain with VAS score of at least 5 during the period of more than 6 months. A total of 188 patients were enrolled into the study, out of which 93 patients were randomly allocated to receive CRF and 95 patients receive PRF treatment. The outcomes of VAS, WOMAC, and SF-12 were measured at baseline, 1 month, 6 months, and 12 months after the treatment. The characteristics of patients at baseline can be viewed in Appendix.

It was observed that the outcome variables contain missing values with different patterns, as displayed in Table 1. There was no information about the reason for each missingness, but it was likely that most of the missing data, particularly for the dropout pattern, can be explained by the therapeutic effect that decreased over time.

Table 1: Missingness pattern

Outcome	Time				Group	
	Baseline	1 month	6 months	12 months	CRF	PRF
VAS	Complete Pattern					
WOMAC	O	O	O	O	57 (61.29%)	36 (37.89%)
	Dropout pattern					
	O	O	O	M	31 (33.33%)	42 (44.21%)
	O	O	M	M	5 (5.38%)	17 (17.89%)
SF-12	Complete Pattern					
	O	O	O	O	56 (60.22%)	34 (35.79%)
	Dropout pattern					
	O	O	O	M	29 (31.18%)	39 (41.05%)
	O	O	M	M	6 (6.45%)	17 (17.89%)
	O	M	M	M	-	1 (1.05%)
	M	M	M	M	-	1 (1.05%)
	Non-monotone pattern					
	O	O	M	O	1 (1.08%)	-
	O	M	O	M	-	1 (1.05%)
	M	O	O	O	-	1 (1.05%)
	M	O	O	M	1 (1.08%)	1 (1.05%)

O = observed, M = missing



## 4 Methodology

### 4.1 Exploratory Data Analysis

Mean profiles within each treatment group for each outcome variable of interest were plotted against each time-point. However, more patients dropped out as time evolved with different rate in both groups, resulting in fewer observations for latter visits. Due to this fact, the plots might not give an appropriate impression and should be interpreted with caution.

### 4.2 Baseline Response Handling

A constrained full likelihood approach in which the baseline value and the post-randomization values are modeled as dependent variables was adopted in this study [9]. The constraint refers to the equality of the baseline mean responses for the treatment groups, which is reasonable due to randomization. In other words, the assumption of equal baseline means is true by design. The parameter estimates and statistical inference under this approach are asymptotically unbiased when there are missing data, assuming missing at random (MAR) mechanism [10]. In addition, unlike another approach which use the baseline as a covariate in the analysis, the interpretation of the treatment effect would be free from conditional interpretation, which prevent the restriction for generalizing the results to replicated trials. When the baseline value is used as part of the inclusion criteria, treating baseline as part of the outcome vector may generate a mixture of normal and truncated normal distributions for the residuals. However, with data in a reasonable range and an adequate sample size, the normality assumption can often be reasonable [11].

### 4.3 Missing Data Handling

According to Mallinckrodt *et al* [12], the potential impact of missing data is best understood by considering the mechanism leading to the missingness. The term missing completely at random (MCAR) refers to the missing data mechanism when missingness does not depend on either the observed or unobserved outcomes; data are missing at random (MAR) if the missingness depends on the observed outcomes, but not the unobserved outcomes; and the mechanism of missing not at random (MNAR) is operating when the missingness also depends on the unobserved outcomes [13,14].

In many settings, the MAR assumption is more reasonable than the MCAR assumption and under this less restrictive assumption, a likelihood-based analysis (also termed ignorable or direct likelihood analysis) provides valid inference. Not only enjoy much wider validity than the simple methods, the ignorable analysis is also simple to conduct without any additional data manipulation and may provide

reasonably stable results. An MAR analysis can be specified *a priori* without additional work relative to a situation with complete data and does not depend on untestable and often implicit assumption regarding the distribution of the unobserved measurements.

However, one cannot rule out the possibility of MNAR data and the bias that can result from it. To explore the impact of deviations from the MAR assumption, a sensitivity analysis can be conducted, within which MNAR models and pattern-mixture models can play a major role [13,14].

Both MAR and MNAR mechanisms are most naturally expressed based on the second factor of the selection modelling framework which is indicated below:

$$f(\mathbf{y}_i, \mathbf{r}_i | X_i, W_i, \boldsymbol{\theta}, \boldsymbol{\psi}) = f(\mathbf{y}_i | X_i, \boldsymbol{\theta})f(\mathbf{r}_i | \mathbf{y}_i, W_i, \boldsymbol{\psi}) \quad (1)$$

where  $\mathbf{y}_i$  is the vector of outcome,  $\mathbf{r}_i$  is the missing data indicators,  $X_i$  and  $W_i$  denote design matrices for the measurement and missingness mechanism, with  $\boldsymbol{\theta}$  and  $\boldsymbol{\psi}$  are their corresponding parameters vectors, respectively. Under MAR and MNAR mechanism, the density of the missingness process can be formulated as in (2) and (3), respectively.

$$f(\mathbf{r}_i | \mathbf{y}_i, W_i, \boldsymbol{\psi}) = f(\mathbf{r}_i | \mathbf{y}_i^o, W_i, \boldsymbol{\psi}) \quad (2)$$

$$f(\mathbf{r}_i | \mathbf{y}_i, W_i, \boldsymbol{\psi}) = f(\mathbf{r}_i | \mathbf{y}_i^o, \mathbf{y}_i^m, W_i, \boldsymbol{\psi}) \quad (3)$$

where  $\mathbf{y}_i^o$  and  $\mathbf{y}_i^m$  are the observed and unobserved (missing) measurement, respectively.

#### 4.4 Multivariate Normal Model (MAR Assumption)

Although the outcome of VAS is naturally an ordinal scale, it can intrinsically be treated as continuous scale, considering the score which ranges from 0 to 10. As argued by Knapp [15], the sample size and distribution are more important than the level of measurement to treat ordinal scale as continuous scale. Treating the ordinal variable as continuous also has advantage in providing more flexibility in the choice of analysis while still preserving the information in the ordering. As for WOMAC, the sum of the separated-index of WOMAC A, WOMAC B, and WOMAC C was taken to create an approximately continuous variable. The outcome of SF-12 was translated into mental component summary (MCS) and physical component summary (PCS) using a devoted algorithm [16], which results can also be considered as continuous variables.

The repeated measures were balanced in this study, in the sense that a common and limited or fixed set of measurement times was considered for all subjects. This

design allows the *a priori* specification of a full multivariate normal model with group-by-time interaction for the fixed effects and unstructured variance-covariance matrix. The randomization allows to draw casual conclusion that the difference can only be due to the variable of interest, which is treatment in this study, assuming the other characteristics at baseline are similar in both treatment groups. Variable time was treated as categorical variable. By doing this, no assumption about the shape of the mean response profile over time is needed [17]. The unstructured covariance was employed since we did not want to make any assumption *a priori* about the correlation for every pair of measurement.

It is worthwhile to note that the term multivariate refers to the fact that the individual measurements at different time-point can be treated as a vector of random variables. Although there are multiple outcomes measured repeatedly within a set of study participants, a joint model for all outcomes simultaneously is not necessarily needed. In this study, the univariate model for each outcome separately may answer the research questions.

Let  $Y_{ij}$  be the outcome variable (VAS, WOMAC, MCS, or PCS) of patient  $i$  at time  $j$  ( $j =$  month 0, 1, 6, and 12),  $x_i$  be the treatment (0 for CRF and 1 for PRF),  $\beta_{0,j}$  and  $\beta_{1,j}$  be fixed effects parameters, the parameterization of the model can be written as follow:

$$Y_{ij} = \beta_{0,j}(1 - x_i) + \beta_{1,j}x_i + \epsilon_{ij} \quad (4)$$

$$\epsilon_{ij} \sim N(0, \Sigma)$$

The normality assumption of residual should be checked to assure the validity of the statistical test. Graphical methods (Q-Q plot and density plot) were used to check the distributional assumption since they are considered as powerful and effective diagnostic tools for checking normality of the data. The Q-Q plot is constructed by plotting the empirical quantiles of the data against the corresponding quantiles of the normal distribution, while the kernel density plot portrays the distribution of the data directly. Large or systematic departures from the line and the bell-shaped curve of normal distribution in the Q-Q plot and kernel density plot, respectively, indicate the abnormality of the data [18].

#### 4.5 Pattern-Mixture Model (MNAR Assumption)

Pattern-mixture models (PMM) can be constructed as a way of exploring the impact of a model and/or selected observations on the inferences made when data are incomplete, or simply as sensitivity analysis [19]. It is a framework that can be considered when the missingness mechanism is MNAR. In PMM, the outcome distribution is modelled conditional on the observed response pattern. PMM decomposes



the joint probability of data and missingness as follow:

$$f(\mathbf{y}_i, \mathbf{r}_i \mid X_i, W_i, \boldsymbol{\theta}, \boldsymbol{\psi}) = f(\mathbf{y}_i \mid \mathbf{r}_i, X_i, \boldsymbol{\theta})f(\mathbf{r}_i \mid W_i, \boldsymbol{\psi}) \quad (5)$$

where the first factor is the density of the measurement process conditional on the missingness process and the second one is the marginal density of the missingness process [13,20,21].

An important issue regarding PMM is that, by definition, it is under-identified because patterns with missing data typically have some parameters that cannot be estimated from the data due to incomplete data within that pattern. One way to overcome this issue is the use of identifying restrictions, which simply indicate from which patterns missing information is borrowed. The complete case missing values (CCMV) specifies that missing information is borrowed from completers (subjects with complete outcome profile); in neighboring case missing values (NCMV), missing information at a time point is borrowed from the nearby pattern for which outcome values are observed at that time point, but unobserved later; and the available case missing value (ACMV) suggests that missing information is borrowed from all available patterns weighted by occurrence of each pattern.

The strategy of using identifying restrictions is implemented as one approach for the sensitivity analysis in this study. The approach is combined with the concept of multiple imputation (MI), in which the identification method is used to determine the conditional distributions of the unobserved outcomes from where the multiple imputations are then drawn. The CCMV (6) and NCMV (7) identifying restrictions which describe MNAR mechanisms were selected to investigate the sensitivity of inferences to departures from MAR.

$$f_t(y_s \mid y_1, \dots, y_{s-1}) = f_T(y_s \mid y_1, \dots, y_{s-1}), \quad s = t + 1, \dots, T \quad (6)$$

$$f_t(y_s \mid y_1, \dots, y_{s-1}) = f_s(y_s \mid y_1, \dots, y_{s-1}), \quad s = t + 1, \dots, T \quad (7)$$

The concept of MI refers to replacing each missing value with a set of  $M$  plausible values. The multiply imputed data sets are then analyzed by using standard procedures for complete data and combining the results from these analyses [13,20]. Twenty five imputations were used in this study. This larger number of imputations than the classic recommendation of three to five imputations is suggested to accommodate the adequacy for other inferential goals such as confidence intervals and p-values, in addition to the point estimates [22,23]. Denote by  $\hat{\boldsymbol{\beta}}^m$  and  $V^m$ , respectively, the estimate of parameter vector  $\boldsymbol{\beta}$  and its covariance matrix from the  $m^{th}$  completed data set ( $m = 1, \dots, M$ ). The MI estimate of  $\boldsymbol{\beta}$  and the measure of its precision are formulated as follows:

$$\hat{\boldsymbol{\beta}}^* = \frac{1}{M} \sum_{m=1}^M \hat{\boldsymbol{\beta}}^m \quad (8)$$

$$W = \frac{1}{M} \sum_{m=1}^M V^m \quad (9)$$

$$B = \frac{1}{M-1} \sum_{m=1}^M (\hat{\beta}^m - \hat{\beta}^*)(\hat{\beta}^m - \hat{\beta}^*)' \quad (10)$$

$$V = W + \left(\frac{M+1}{M}\right)B \quad (11)$$

Equation (8), (9), (10), and (11) are the equations for MI estimate of  $\beta$ , within-imputation covariance matrix, between-imputation covariance matrix, and the estimate of the covariance matrix of  $\hat{\beta}^*$ , respectively. To test the null hypothesis that a parameter is equal to a specific value ( $\beta = \beta_0$ ), the following statistics can be used:

$$t_v = \frac{\hat{\beta}^* - \beta_0}{\sqrt{V}} \quad (12)$$

The statistics has a  $t$ -distribution with the adjusted  $v$  degrees of freedom, as formulated below:

$$v = (M-1) \left[1 + \frac{W}{\left(1 + \frac{1}{M}\right)B}\right]^2 \quad (13)$$

However, equation (13) can create a clearly inappropriate situation where the values produced are larger than the degrees of freedom in the complete data. Therefore, the adjusted degrees of freedom as formulated below were used in the analysis:

$$v^* = \left[\frac{1}{v} + \frac{1}{v_{obs}}\right]^{-1} \quad (14)$$

$$v_{obs} = \frac{(1-\gamma)v_{com}(v_{com}+1)}{(v_{com}+3)} \quad (15)$$

$$\gamma = \frac{\left(1 + \frac{1}{M}\right)B}{V} \quad (16)$$

where  $v_{com}$  is the degrees of freedom of  $\hat{\beta}^*$  in the hypothetically complete data and  $\gamma$  is the proportion of the variation attributable to the missing data. In models that fit  $k$  parameters on data with a sample size of  $n$ ,  $v_{com} = n - k$ . When there is no missing information about one parameter,  $\gamma$  is equal to 0 and  $v = v_{com}$  [24].

## 4.6 Software

The data analysis for this master's thesis was generated using SAS software, Version 9.4 of the SAS System for Windows. Copyright ©2017 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary NC, USA. All statistical analysis were performed at significance level of 0.05.



## 5 Results

### 5.1 Exploratory Data

The plots of mean profile against each time-point, together with their corresponding 95% confidence intervals, for each outcome variable of interest are displayed in Figure 1.

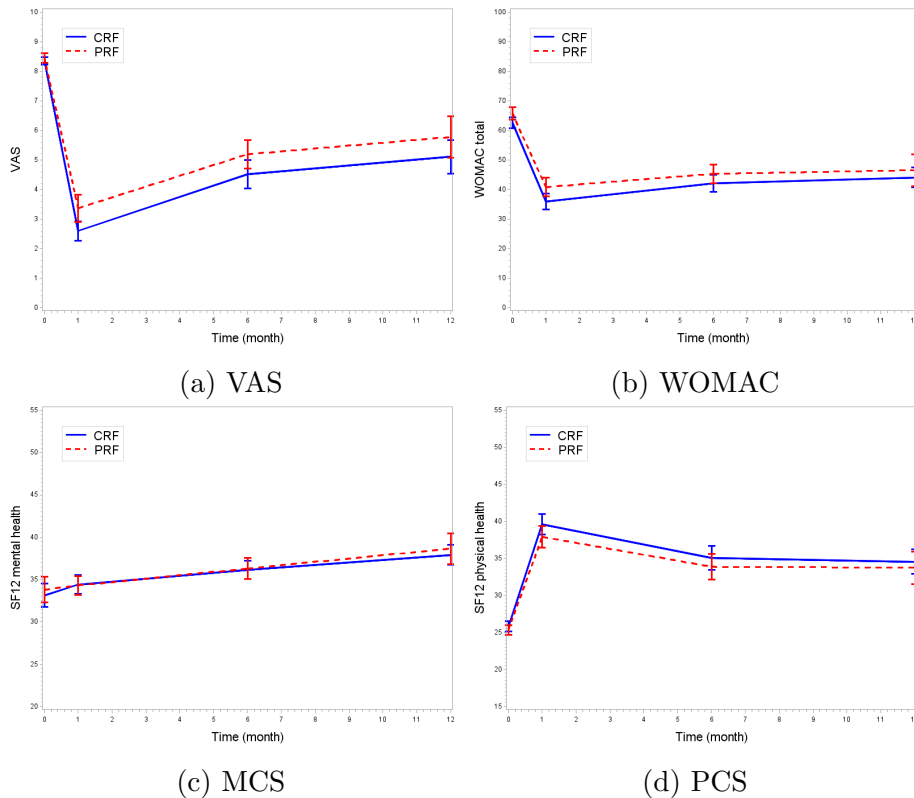


Figure 1: Mean profile

As mentioned earlier, these plots should be interpreted with caution due to many missing values in both treatment groups as time evolved. From the plots, we merely see the trend of each outcome variable over time of the patients who were still in the study as time progressed and we cannot get the idea about what would be happening had nobody dropout. The VAS and WOMAC score tended to decrease in the first month after treatment for both groups and increased again after 6 and 12 months, respectively. The MCS showed slightly increasing trend and the curve for both groups almost coincided. In contrast to VAS and WOMAC, the PCS score increased in the first month after treatment and declined afterwards. The 95% confidence intervals for the point estimates tended to be wider at the latter time-point due to the dropouts. In addition, the wider intervals were observed in the PRF group because there were more dropouts in that group compared to the CRF group.

## 5.2 VAS

Table 2 summarizes the parameter estimates and their corresponding standard errors for the outcome VAS from the multivariate normal model and pattern-mixture models using identifying restrictions CCMV and NCMV.

Table 2: VAS: Parameter estimates (standard errors) resulting from the multivariate normal model (MVN) and pattern-mixture model using identifying restrictions CCMV and NCMV

Effect	Parameter	MVN	CCMV	NCMV
Parameter estimate (SE)				
CRF0	$\beta_{0,0}$	8.3548 (0.0729)	8.3548 (0.0729)	8.3548 (0.0729)
CRF1	$\beta_{0,1}$	2.6022 (0.2007)	2.6022 (0.2007)	2.6022 (0.2007)
CRF6	$\beta_{0,6}$	4.8449 (0.3044)	4.4847 (0.2248)	4.6942 (0.2288)
CRF12	$\beta_{0,12}$	7.2404 (0.4287)	5.6890 (0.2654)	5.7656 (0.2591)
PRF0	$\beta_{1,0}$	8.4526 (0.0721)	8.4526 (0.0721)	8.4526 (0.0721)
PRF1	$\beta_{1,1}$	3.3684 (0.1986)	3.3684 (0.1986)	3.3684 (0.1986)
PRF6	$\beta_{1,6}$	6.2985 (0.3096)	5.0021 (0.2398)	5.5857 (0.2292)
PRF12	$\beta_{1,12}$	9.5189 (0.4605)	6.6131 (0.2668)	6.7663 (0.3210)
<b>Mean difference between CRF and PRF group</b>				
time 0	$\beta_{0,0} - \beta_{1,0}$	-0.0978 (0.1025)	-0.0978 (0.1025)	-0.0978 (0.1025)
time 1	$\beta_{0,1} - \beta_{1,1}$	-0.7663 (0.2824)	-0.7663 (0.2824)	-0.7663 (0.2824)
time 6	$\beta_{0,6} - \beta_{1,6}$	-1.4536 (0.4342)	-0.5174 (0.3243)	-0.8915 (0.3233)
time 12	$\beta_{0,12} - \beta_{1,12}$	-2.2786 (0.6292)	-0.9240 (0.3430)	-1.0007 (0.3726)
<b>p-value for the mean difference between CRF and PRF group</b>				
time 0		0.3413	0.3413	0.3413
time 1		0.0073	0.0073	0.0073
time 6		0.0012	0.1126	0.0064
time 12		0.0007	0.0082	0.0089

The mean plots of VAS at each time-point by treatment, after multiple imputation using the CCMV and NCMV strategy, are displayed in Figure 2, together with the result from the multivariate normal model. From the plots it seems that there was no difference in the average of VAS between two treatment groups at baseline. At the first month, the average of VAS decreased in both groups, but it seems that the decrease in CRF group was greater than PRF group. The average of VAS increased again at month 6 and 12 after treatment, respectively, in the two groups. Remarkable contrast at the end of evaluation between both groups was observed in the plot of the multivariate normal model. The CCMV and NCMV identifying restrictions demonstrated similar difference between the two treatment groups at month 12, but small discrepancy at the sixth month.

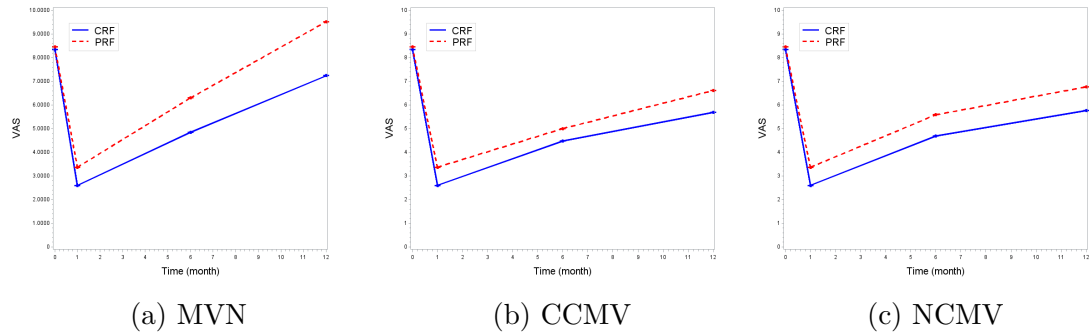


Figure 2: VAS sensitivity analysis

### 5.3 WOMAC

The parameter estimates and their corresponding standard errors for the outcome WOMAC are presented in Table 3. The parameter estimates from the sensitivity analysis using identifying restrictions CCMV and NCMV are also presented to compare the results.

Table 3: WOMAC: Parameter estimates (standard errors) resulting from the multivariate normal model (MVN) and pattern-mixture model using identifying restrictions CCMV and NCMV

Effect	Parameter	MVN	CCMV	NCMV
Parameter estimate (SE)				
CRF0	$\beta_{0,0}$	62.5699 (0.9922)	62.5699 (0.9922)	62.5699 (0.9922)
CRF1	$\beta_{0,1}$	35.9355 (1.4595)	35.9355 (1.4595)	35.9355 (1.4595)
CRF6	$\beta_{0,6}$	43.7442 (1.7399)	43.1045 (1.5000)	43.4490 (1.5991)
CRF12	$\beta_{0,12}$	52.2667 (2.0676)	51.2280 (2.0618)	51.5178 (2.0343)
PRF0	$\beta_{1,0}$	65.7789 (0.9817)	65.7789 (0.9817)	65.7789 (0.9817)
PRF1	$\beta_{1,1}$	40.8316 (1.4441)	40.8316 (1.4441)	40.8316 (1.4441)
PRF6	$\beta_{1,6}$	50.7709 (1.7543)	48.1175 (1.5611)	49.6349 (1.6327)
PRF12	$\beta_{1,12}$	61.8409 (2.2227)	59.0480 (2.3627)	59.7074 (2.1622)
<b>Mean difference between CRF and PRF group</b>				
time 0	$\beta_{0,0} - \beta_{1,0}$	-3.2091 (1.3957)	-3.2091 (1.3957)	-3.2091 (1.3957)
time 1	$\beta_{0,1} - \beta_{1,1}$	-4.8961 (2.0532)	-4.8961 (2.0532)	-4.8961 (2.0532)
time 6	$\beta_{0,6} - \beta_{1,6}$	-7.0267 (2.4708)	-5.0130 (2.1456)	-6.1859 (2.2578)
time 12	$\beta_{0,12} - \beta_{1,12}$	-9.5742 (3.0357)	-7.8200 (2.6629)	-8.1895 (2.6044)
<b>p-value for the mean difference between CRF and PRF group</b>				
time 0		0.0226	0.0226	0.0226
time 1		0.0181	0.0181	0.0181
time 6		0.0051	0.0207	0.0068
time 12		0.0021	0.0039	0.0020

Figure 3 shows the mean profile of WOMAC against each time-point by treat-

ment group after multiple imputation using the CCMV and NCMV strategy, respectively, was conducted. The profile after fitting the multivariate normal model is also displayed. The plots indicate that there was a little difference in the average of WOMAC at baseline between CRF and PRF groups. The average of the score decreased at the first month after treatment and the difference between groups seemed to be larger. At month 6 and 12, the WOMAC score was higher than the first month and the difference between two groups was slightly larger when multivariate normal model was fitted.

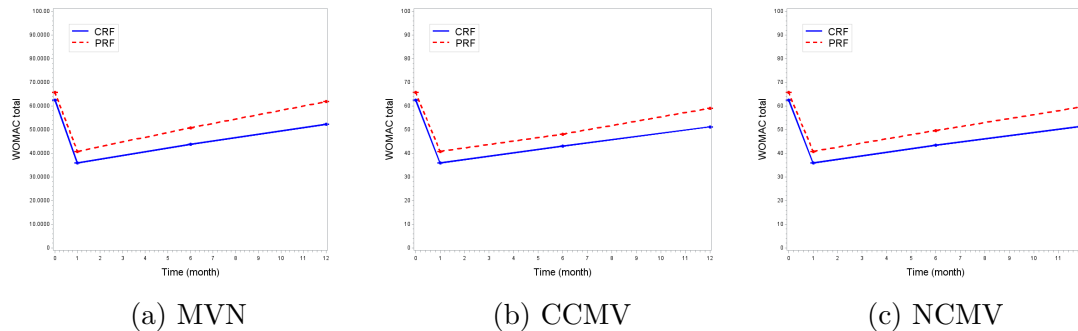


Figure 3: WOMAC sensitivity analysis

## 5.4 SF-12 MCS and PCS

Table 4 and 5 display the parameter estimates along with their corresponding standard errors as well as the treatment differences for the SF-12 mental and physical health summary scales, respectively. The results from the primary analysis and sensitivity analysis are tabulated altogether. In addition, the mean profile of MCS and PCS against each time-point by treatment group after being extrapolated using CCMV and NCMV strategy can be seen in Figure 4 and 5, respectively. The profile after fitting the multivariate normal model is also displayed. From the MCS plots, it seems that the curves of both treatment groups almost coincided, indicating that there was no difference between them at each time-point. Meanwhile, in the PCS plots, there was slightly difference between the curves of CRF and PRF at each time-point, but at baseline.

Table 4: MCS from SF-12: Parameter estimates (standard errors) resulting from the multivariate normal model (MVN) and pattern-mixture model using identifying restrictions CCMV and NCMV

Effect	Parameter	MVN	CCMV	NCMV
Parameter estimate (SE)				
CRF0	$\beta_{0,0}$	33.0342 (0.7223)	33.0413 (0.7225)	33.0413 (0.7225)
CRF1	$\beta_{0,1}$	34.4256 (0.5416)	34.4256 (0.5421)	34.4256 (0.5421)
CRF6	$\beta_{0,6}$	35.8633 (0.5740)	35.8606 (0.5687)	35.8921 (0.5784)
CRF12	$\beta_{0,12}$	36.9215 (0.6156)	36.8674 (0.5963)	36.8785 (0.5973)
PRF0	$\beta_{1,0}$	33.6876 (0.7207)	33.7018 (0.7186)	33.7018 (0.7186)
PRF1	$\beta_{1,1}$	34.1937 (0.5416)	34.1770 (0.5407)	34.1770 (0.5407)
PRF6	$\beta_{1,6}$	35.3636 (0.5863)	35.2848 (0.5722)	35.2982 (0.5888)
PRF12	$\beta_{1,12}$	36.6943 (0.7008)	36.6722 (0.6095)	36.6769 (0.6116)
<b>Mean difference between CRF and PRF group</b>				
time 0	$\beta_{0,0} - \beta_{1,0}$	-0.6533 (1.0204)	-0.6605 (1.0187)	-0.6605 (1.0187)
time 1	$\beta_{0,1} - \beta_{1,1}$	0.2319 (0.7659)	0.2486 (0.7656)	0.2486 (0.7656)
time 6	$\beta_{0,6} - \beta_{1,6}$	0.4997 (0.8206)	0.5758 (0.8085)	0.5939 (0.8283)
time 12	$\beta_{0,12} - \beta_{1,12}$	0.2273 (0.9328)	0.1952 (0.8484)	0.2015 (0.8518)
<b>p-value for the mean difference between CRF and PRF group</b>				
time 0		0.5228	0.5176	0.5176
time 1		0.7624	0.7458	0.7458
time 6		0.5433	0.4774	0.4744
time 12		0.8079	0.8184	0.8133

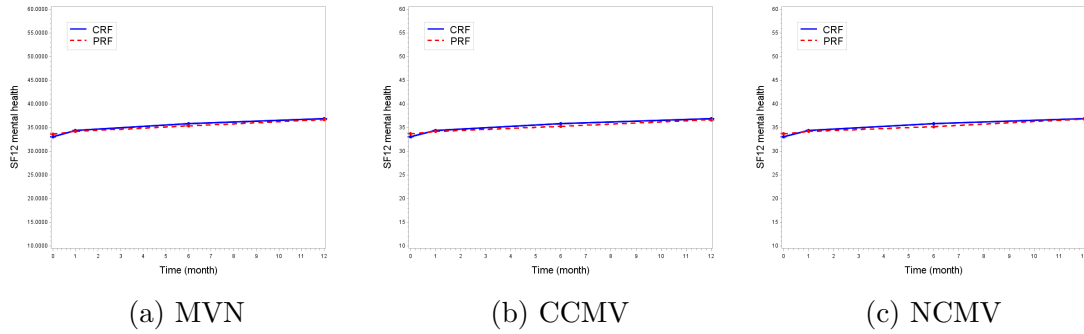


Figure 4: MCS sensitivity analysis



Table 5: PCS from SF-12: Parameter estimates (standard errors) resulting from the multivariate normal model (MVN) and pattern-mixture model using identifying restrictions CCMV and NCMV

Effect	Parameter	MVN	CCMV	NCMV
Parameter estimate (SE)				
CRF0	$\beta_{0,0}$	25.8039 (0.3303)	25.8099 (0.3306)	25.8099 (0.3306)
CRF1	$\beta_{0,1}$	39.6063 (0.7055)	39.6063 (0.7049)	39.6063 (0.7049)
CRF6	$\beta_{0,6}$	34.3099 (0.8739)	34.6510 (0.7770)	34.3769 (0.8176)
CRF12	$\beta_{0,12}$	31.9050 (0.8652)	32.0001 (0.8020)	31.9065 (0.8137)
PRF0	$\beta_{1,0}$	25.3563 (0.3298)	25.3666 (0.3290)	25.3666 (0.3290)
PRF1	$\beta_{1,1}$	37.8952 (0.7061)	37.8706 (0.7036)	37.8706 (0.7036)
PRF6	$\beta_{1,6}$	31.7637 (0.8950)	33.0541 (0.7828)	31.9646 (0.8161)
PRF12	$\beta_{1,12}$	28.8679 (1.0235)	29.4289 (0.8322)	29.0570 (0.8431)
<b>Mean difference between CRF and PRF group</b>				
time 0	$\beta_{0,0} - \beta_{1,0}$	0.4476 (0.4668)	0.4433 (0.4664)	0.4433 (0.4664)
time 1	$\beta_{0,1} - \beta_{1,1}$	1.7111 (0.9981)	1.7358 (0.9960)	1.7358 (0.9960)
time 6	$\beta_{0,6} - \beta_{1,6}$	2.5463 (1.2510)	1.5969 (1.1069)	2.4123 (1.1580)
time 12	$\beta_{0,12} - \beta_{1,12}$	3.0371 (1.3402)	2.5712 (1.1495)	2.8495 (1.1663)
<b>p-value for the mean difference between CRF and PRF group</b>				
time 0		0.3389	0.3432	0.3432
time 1		0.0881	0.0831	0.0831
time 6		0.0436	0.1510	0.0387
time 12		0.0258	0.0274	0.0161

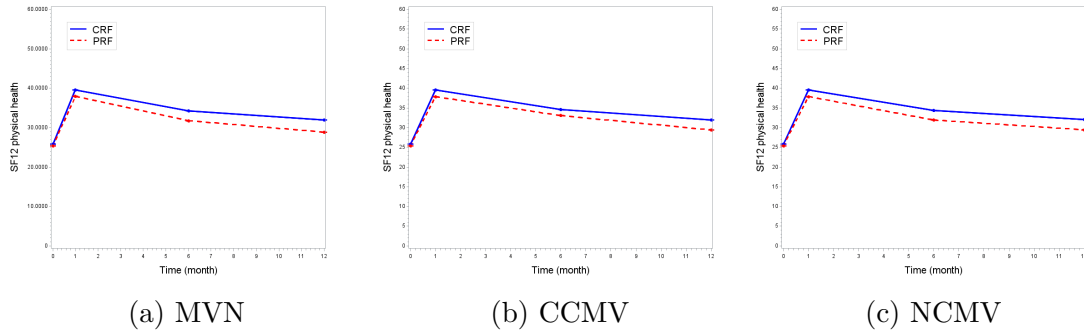


Figure 5: PCS sensitivity analysis

## 6 Discussion

### 6.1 VAS

VAS is a unidimensional measure of pain intensity, generally considered as a continuous scale comprised of a horizontal or vertical 10-cm line, anchored by 2 verbal descriptors: "no pain" (score of 0) and "worst imaginable pain" (score of 10) [25]. As previously stated, in this study the outcome VAS was scored in an ordinal manner rather than in continuous form. This practice may explain the appearance of the Q-Q plot which trended to be linear and yet it was wiggly due to lot of residuals with the same values. Nevertheless, the histogram showing the distribution of the residuals is reasonably symmetric, supporting the decision to treat VAS as continuous variable in the analysis.

From the multivariate model, it was observed that there was no significant difference of VAS score between patients in CRF and PRF group, while statistically significant differences were noticed at 1 month, 6 months, and 12 months after the treatment. The VAS score declined noticeably at the first month for both treatment groups, then gradually increased again at month 6 and 12, respectively. It is worthwhile to mention that the score change is still clinically important up to the sixth month for both treatment groups [26].

Since there was no dropout at baseline and at the first month of the measurement, the parameter estimates from the multivariate model and pattern-mixture models showed identical results. At month 6 there were less dropouts in the CRF group compared to PRF group, which explains similar parameter estimates of the mean in this group ( $\beta_{0,6}$ ) obtained from fitting the multivariate model as well as after multiple imputation using the identifying restrictions CCMV and NCMV were conducted. On the other hand, the parameter estimates in the PRF group ( $\beta_{1,6}$ ) obtained after extrapolation using CCMV were lower than the estimates from the multivariate model. This situation leads to the underestimation and non-significance of the mean difference between the CRF and PRF groups.

As mentioned earlier, the dropouts might be explained by the decreasing treatment effect over time, thus it seems unlikely to expect better score in the VAS outcome for the patients who dropped out. Hence, the CCMV approach might be less appropriate since this strategy always refers to the best group, *i.e.* the one with the best prognosis.

The NCMV extrapolation might be more plausible since the information was borrowed from the nearest pattern, which referred to the patients who had measurement at month 6 and dropped out at month 12. This hypothesis was supported by the higher treatment difference between CRF and PRF compared to the one obtained

using CCMV. The treatment difference was now also significant at month 6, in agreement with the conclusion obtained from the multivariate model.

Since more patients dropped out in both groups at 12 months after treatment, the parameter estimates ( $\beta_{0,12}$  and  $\beta_{1,12}$ ) were now underestimated in the two treatment groups when CCMV as well as NCMV strategy were applied. Despite the same conclusion with the result from multivariate model regarding the significance mean difference between the two groups, the point estimates were slightly different. This result suggests caution concerning the conclusion obtained under the multivariate model. It is implied that higher difference between treatment groups was obtained should the MAR assumption hold.

## 6.2 WOMAC

WOMAC is a self-report questionnaire to assess pain, stiffness, and physical function in patients with hip and/or knee osteoarthritis. It consists of 24 items divided into 3 subscales: 5 items of pain, 2 items of stiffness, and 17 items of physical function. In this study, the Likert scale version corresponds to an ordinal scale of 0-4 was used to score each subscales, resulting in possible sum which ranges between 0 to 96. The higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations [27].

As mentioned earlier, the sum of the subscales of WOMAC was taken to create an approximately continuous variable, rather than treating the ordinal scale for each subscales. Indeed, the normality assumption checking as shown in the Appendix (Figure 7) seems realistic for this outcome. Despite the randomization process, there was significant difference between groups at baseline, where the patients in CRF treatment group had lower scores compared to those in PRF treatment group. The WOMAC scores significantly decreased in the first month after treatment for both groups and the mean changes of the scores from baseline at this time-point differed significantly for patients in both groups. The WOMAC scores tended to increase again at 6 months and 12 months after treatment in both groups, though they were still significantly lower than the corresponding scores at baseline. The mean changes of the scores at these time-points also differed significantly for patients in both treatment groups. Following the suggestion from White *et al* [28], the decreasing score of WOMAC in this study also showed clinically important improvement until 6 months after treatment for both groups.

Since there was no missing value at baseline and at the first month of the evaluation, the parameter estimates from the multivariate model and pattern-mixture models showed identical results. Since it was assumed that patients in the study dropped out mainly because of the decreasing therapeutic effect over time, the strategy of

CCMV referred to the one with better prognosis. Considering that more patients in PRF group dropped out at month 6 compared to the patients in CRF group, the CCMV extrapolated rather towards a decline in PRF group, producing less treatment difference at month 6. In this sense, the NCMV approach was likely to be better since the information was borrowed from the nearest pattern and the estimations seemed to be more similar to the multivariate model obtained under MAR assumption, which used all the available data to compensate for the data missing on a particular patient. Nevertheless, the conclusion of significance between the three models were the same, in which there were significant differences of mean change of WOMAC score between patients receiving CRF and PRF at each time-point of evaluation.

### 6.3 SF-12 MCS and PCS

The SF-12 is a shorter, yet valid, alternative to the SF-36, a popular generic health status measure in a wide variety of patient groups and social surveys. It contains the measurement of eight concepts commonly represented in widely used surveys: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. From this instrument, a mental component summary scale score (MCS) and physical component summary scale score (PCS) can be generated. General health and vitality are domains shared by MCS and PCS. In addition, MCS encompasses social functioning, role limitations due to emotional problems, and mental health; whereas the remaining items are incorporated in the PCS. The SF-12 MCS and PCS range from 0 to 100, with higher scores indicating better self-reported health condition [16,29].

Both MCS and PCS were treated as continuous variables and the graphical methods presented in the Appendix (Figure 8 and 9) show that the residuals for both outcomes were approximately normal. The analysis showed that there was no significant difference between CRF and PRF treatment in the mean changes of MCS at each time-point of evaluation. The result was also confirmed in the sensitivity analysis, using both CCMV and NCMV identifying restrictions.

Notwithstanding the result of MCS, there were significant treatment difference of PCS at 6 and 12 months after treatment, respectively. However, the sensitivity analysis using CCMV showed different conclusion at the sixth month. The average of PCS in the PRF group at this time-point was extrapolated towards a higher value since CCMV referred to the patients with better prognosis, leading to smaller difference between the two treatment groups. The NCMV identifying restrictions seemed to be more realistic and provided similar conclusion with the primary analysis under MAR assumption.

It is also important to note that there were several non-monotone missingness patterns for the measurement of SF-12. For these cases, partial imputation step under MAR assumption was performed before the pattern-mixture based imputation. It can be argued as a reasonable assumption that patients tend to miss the intermediate visits due to reasons unrelated to their medical condition under study, even if the rest of the missing data (monotone patterns) will then be imputed based on different assumptions. Moreover, very small proportion of non-monotone missing data will typically have a small effect on the results of analysis and imputing these values under the MAR assumption should not compromise the validity of the sensitivity analysis [30].

## 7 Concluding Remarks

The objective of this study is to compare the efficacy of CRF and PRF treatment in alleviating pain and functional impairment in patients with advanced osteoarthritis, as measured using VAS, WOMAC, and SF-12. By taking the missingness in the data into account, the mean changes of VAS and WOMAC from baseline differ statistically significant for patients receiving CRF versus PRF treatment at each evaluation time-point (month 1, 6, and 12 after treatment). There is also statistically significant difference in the PCS outcome at month 6 and 12 after treatment. In general the patients receiving CRF showed better results compared to those receiving PRF. In contrast, patients in both groups did not show any significant difference for the outcome of MCS.

It was seen from the result of sensitivity analysis that the CCMV approach might produce result that can be optimistic and misleading for the general study population due to the natural assumption that the completers, from where the information was borrowed, were more likely to achieve better prognosis. The sensitivity analysis using NCMV extrapolation seemed to be more plausible, which was also shown by the same conclusions for the analysis of all outcomes.

The analysis method used in this report might have limitation. As mentioned in the previous section, the response variable VAS can be considered as in between category and continuous type. Although the analysis method for continuous data seemed reasonable, proper normal distribution may not be expected. The method for ordinal outcome, such as proportional odds model, can be considered as an alternative. However, this model may create a misleading impression about the relationship between the outcome and explanatory variables if the underlying assumptions are violated. Meanwhile, switching to other model that has far more parameters than is necessary is not ideal solution either. It is recommended for future study that uses the same pain measurement tool to adopt the original idea of the assessment, in which the continuous instead of discrete values used in the scoring process.

It can be argued that analysis from an adequate randomized trial need not be adjusted because the analysis will result in a valid estimate of the treatment effect. Another important reason not to include the covariates at baseline in this analysis was due to the absence of any specific prognostic variables considered or known to influence the result. It may be advised for further study to take important prognostic factors into consideration before starting the trial as well as to assess and adjust those factors in order to obtain more precise estimate of the effect [31].

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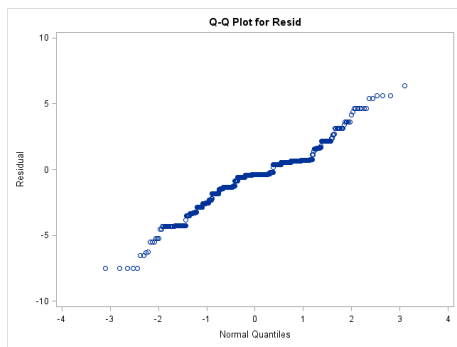


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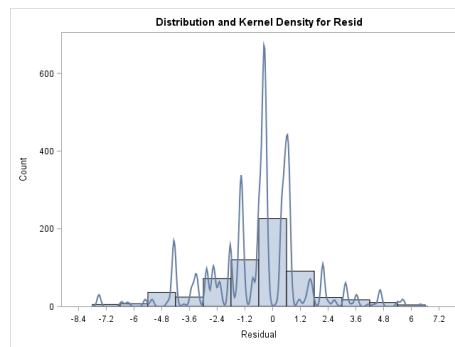
## Appendix—Table and Figures

Table 6: Characteristics of patients at baseline

Characteristics	CRF treatment	PRF treatment
Age (years) (mean $\pm$ SD)	73.05 $\pm$ 9.89	74.12 $\pm$ 9.23
Sex:		
Male (n)	12	16
Female (n)	81	79
BMI ( $kg/m^2$ ) (mean $\pm$ SD)	30.10 $\pm$ 3.17	30.86 $\pm$ 4.02
VAS (mean $\pm$ SD)	8.35 $\pm$ 0.62	8.45 $\pm$ 0.78
WOMAC total (mean $\pm$ SD)	62.57 $\pm$ 9.08	65.78 $\pm$ 10.12
SF-12 mental score (mean $\pm$ SD)	33.14 $\pm$ 6.69	33.81 $\pm$ 7.18
SF-12 physical score (mean $\pm$ SD)	25.82 $\pm$ 3.26	25.36 $\pm$ 3.12

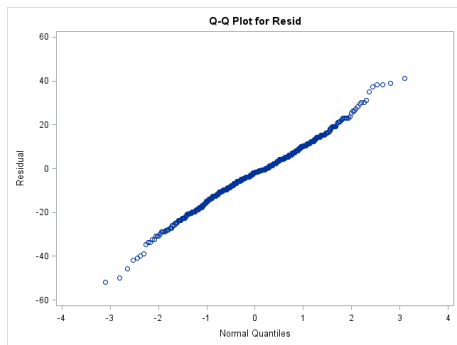


(a) QQ plot

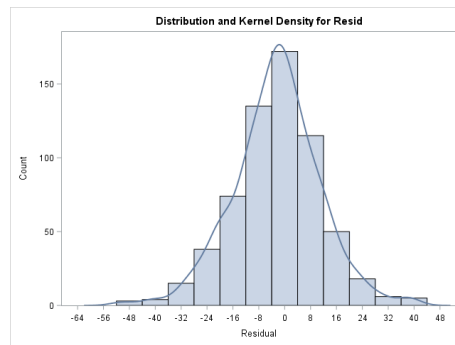


(b) Kernel density plot

Figure 6: Normality assumption test for VAS

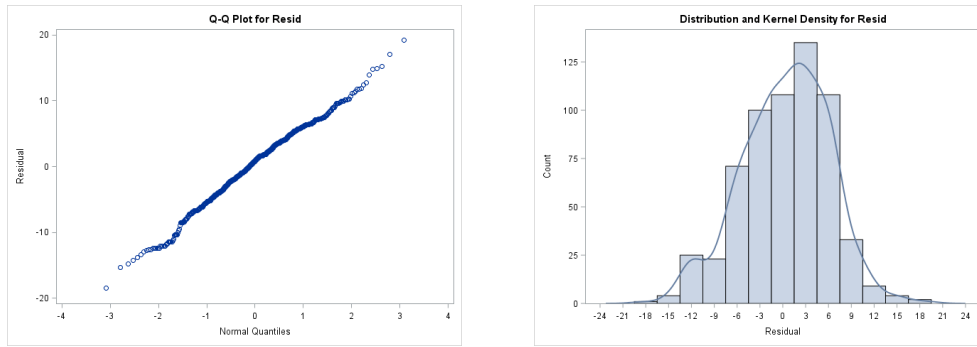


(a) QQ plot



(b) Kernel density plot

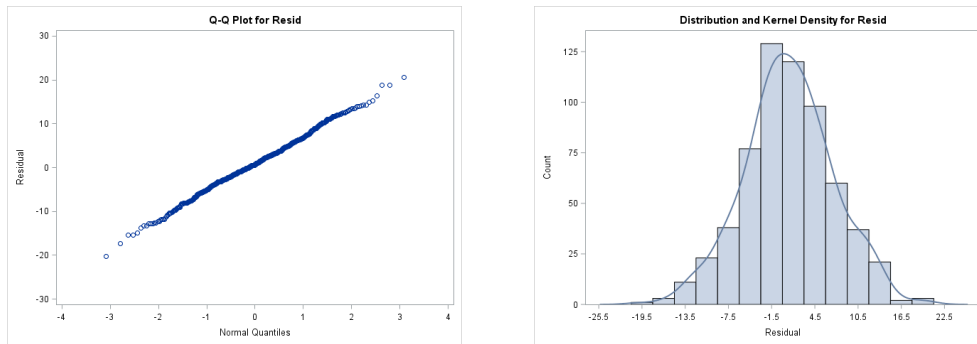
Figure 7: Normality assumption test for WOMAC



(a) QQ plot

(b) Kernel density plot

Figure 8: Normality assumption test for MCS



(a) QQ plot

(b) Kernel density plot

Figure 9: Normality assumption test for PCS

## Appendix—SAS code

VAS

```
proc mixed data=vas.vas method=ml; class therapy id_no time;
model vas = therapy*time / noint s residual cl ddfm=sat outpm=vas.predict;
repeated time / subject=id_no type=un r rcorr;
estimate 'time 0' therapy*time 1 0 0 0 -1 0 0 0;
estimate 'time 1' therapy*time 0 1 0 0 0 -1 0 0;
estimate 'time 6' therapy*time 0 0 1 0 0 0 -1 0;
estimate 'time 12' therapy*time 0 0 0 1 0 0 0 -1; run;

proc mi data=vas.vas_wide seed=123 out=vas.vas_ccmv simple maximum=2.3;
class therapy; var therapy log_vas0 log_vas1 log_vas6 log_vas12;
monotone reg; mmar model(log_vas6 log_vas12 / modelobs=ccmv); run;

proc mixed data=vas.vas_ccmv_long method=ml asycov;
class therapy id_no time; by _imputation_;
model vas = therapy*time / noint s residual cl covb ddfm=sat;
repeated time / subject=id_no type=un r rcorr;
estimate 'time 0' therapy*time 1 0 0 0 -1 0 0 0;
estimate 'time 1' therapy*time 0 1 0 0 0 -1 0 0;
estimate 'time 6' therapy*time 0 0 1 0 0 0 -1 0;
estimate 'time 12' therapy*time 0 0 0 1 0 0 0 -1;
ods output SolutionF=vas.solution_ccmv; ods output CovB=vas.covb_ccmv;
ods output covparms=vas.covparm_ccmv; ods output estimates=vas.estimate_ccmv;
```

```

ods output asycov=vas.asycov_ccmv; run;

proc mianalyze parms=vas.solution_ccmv edf=180 covb(effectvar=rowcol)=vas.covb_ccmv;
class therapy time; modeleffects therapy*time; run;

data vas.estimate_ccmv; set vas.estimate_ccmv;
if Label='time 0' then effect='t1'; if Label='time 1' then effect='t2';
if Label='time 6' then effect='t3'; if Label='time 12' then effect='t4';
proc mianalyze parms=vas.estimate_ccmv edf=180; modeleffects t1 t2 t3 t4; run;

proc mi data=vas.vas_wide seed=123 out=vas.vas_ncmv simple maximum=2.3;
class therapy; var therapy log_vas0 log_vas1 log_vas6 log_vas12;
monotone reg; mmar model(log_vas6 log_vas12 / modelobs=ncmv); run;

proc mixed data=vas.vas_ncmv_long method=ml asycov;
class therapy id_no time; by _imputation_;
model vas = therapy*time / noint s residual cl covb ddfm=sat;
repeated time / subject=id_no type=un r rcorr;
estimate 'time 0' therapy*time 1 0 0 0 -1 0 0 0;
estimate 'time 1' therapy*time 0 1 0 0 0 -1 0 0;
estimate 'time 6' therapy*time 0 0 1 0 0 0 -1 0;
estimate 'time 12' therapy*time 0 0 0 1 0 0 0 -1;
ods output SolutionF=vas.solution_ncmv; ods output CovB=vas.covb_ncmv;
ods output covparms=vas.covparm_ncmv; ods output estimates=vas.estimate_ncmv;
ods output asycov=vas.asycov_ncmv; run;

proc mianalyze parms=vas.solution_ncmv edf=180 covb(effectvar=rowcol)=vas.covb_ncmv;
class therapy time; modeleffects therapy*time; run;

data vas.estimate_ncmv; set vas.estimate_ncmv;
if Label='time 0' then effect='t1'; if Label='time 1' then effect='t2';
if Label='time 6' then effect='t3'; if Label='time 12' then effect='t4';
proc mianalyze parms=vas.estimate_ncmv edf=180; modeleffects t1 t2 t3 t4; run;

WOMAC

proc mixed data=womac.womac method=ml; class therapy id_no time;
model womac = therapy*time / noint s residual cl ddfm=sat outpm=womac.predict;
repeated time / subject=id_no type=un r rcorr;
estimate 'time 0' therapy*time 1 0 0 0 -1 0 0 0;
estimate 'time 1' therapy*time 0 1 0 0 0 -1 0 0;
estimate 'time 6' therapy*time 0 0 1 0 0 0 -1 0;
estimate 'time 12' therapy*time 0 0 0 1 0 0 0 -1; run;

proc mi data=womac.womac_wide seed=123 out=womac.womac_ccmv simple maximum=96;
class therapy; var therapy womac0 womac1 womac6 womac12;
monotone reg; mmar model(womac6 womac12 / modelobs=ccmv); run;

proc mixed data=womac.womac_ccmv_long method=ml asycov;
class therapy id_no time; by _imputation_;
model womac = therapy*time / noint s residual cl covb ddfm=sat;
repeated time / subject=id_no type=un r rcorr;
estimate 'time 0' therapy*time 1 0 0 0 -1 0 0 0;
estimate 'time 1' therapy*time 0 1 0 0 0 -1 0 0;
estimate 'time 6' therapy*time 0 0 1 0 0 0 -1 0;
estimate 'time 12' therapy*time 0 0 0 1 0 0 0 -1;
ods output SolutionF=womac.solution_ccmv; ods output CovB=womac.covb_ccmv;
ods output covparms=womac.covparm_ccmv; ods output estimates=womac.estimate_ccmv;
ods output asycov=womac.asycov_ccmv; run;

proc mianalyze parms=womac.solution_ccmv edf=180 covb(effectvar=rowcol)=womac.covb_ccmv;
class therapy time; modeleffects therapy*time; run;

data womac.estimate_ccmv; set womac.estimate_ccmv;

```

```

if Label='time 0' then effect='t1'; if Label='time 1' then effect='t2';
if Label='time 6' then effect='t3'; if Label='time 12' then effect='t4';
proc mianalyze parms=womac.estimate_ccmv edf=180; modeleffects t1 t2 t3 t4; run;

proc mi data=womac.womac_wide seed=123 out=womac.womac_ncmv simple maximum=96;
class therapy; var therapy womac0 womac1 womac6 womac12;
monotone reg; mmar model(womac6 womac12 / modelobs=ncmv); run;

proc mixed data=womac.womac_ncmv_long method=ml asycov;
class therapy id_no time; by _imputation_;
model womac = therapy*time / noint s residual cl covb ddfm=sat;
repeated time / subject=id_no type=un r rcorr;
estimate 'time 0' therapy*time 1 0 0 0 -1 0 0 0;
estimate 'time 1' therapy*time 0 1 0 0 0 -1 0 0;
estimate 'time 6' therapy*time 0 0 1 0 0 0 -1 0;
estimate 'time 12' therapy*time 0 0 0 1 0 0 0 -1;
ods output SolutionF=womac.solution_ncmv; ods output CovB=womac.covb_ncmv;
ods output covparms=womac.covparm_ncmv; ods output estimates=womac.estimate_ncmv;
ods output asycov=womac.asycov_ncmv; run;

proc mianalyze parms=womac.solution_ncmv edf=180 covb(effectvar=rowcol)=womac.covb_ncmv;
class therapy time; modeleffects therapy*time; run;

data womac.estimate_ncmv; set womac.estimate_ncmv;
if Label='time 0' then effect='t1'; if Label='time 1' then effect='t2';
if Label='time 6' then effect='t3'; if Label='time 12' then effect='t4';
proc mianalyze parms=womac.estimate_ncmv edf=180; modeleffects t1 t2 t3 t4; run;

MCS score from SF-12

proc mixed data=sfm.sf_mental method=ml; class therapy id_no time;
model sf12_mental = therapy*time / noint s residual cl ddfm=sat outpm=sfm.predict;
repeated time / subject=id_no type=un r rcorr;
estimate 'time 0' therapy*time 1 0 0 0 -1 0 0 0;
estimate 'time 1' therapy*time 0 1 0 0 0 -1 0 0;
estimate 'time 6' therapy*time 0 0 1 0 0 0 -1 0;
estimate 'time 12' therapy*time 0 0 0 1 0 0 0 -1; run;

proc mi data=sfm.sfm_wide seed=123 out=sfm.sfm_mono simple maximum=100;
var therapy sfm0 sfm1 sfm6 sfm12; mcmc impute=monotone; run;

proc mi data=sfm.sfm_mono seed=123 out=sfm.sfm_ccmv simple nimpute=1 maximum=100;
class therapy; var therapy sfm0 sfm1 sfm6 sfm12;
monotone reg; mmar model(sfm6 sfm12 / modelobs=ccmv); run;

proc mixed data=sfm.sfm_ccmv_long method=ml asycov;
class therapy id_no time; by _imputation_;
model sfm = therapy*time / noint s residual cl covb ddfm=sat;
repeated time / subject=id_no type=un r rcorr;
estimate 'time 0' therapy*time 1 0 0 0 -1 0 0 0;
estimate 'time 1' therapy*time 0 1 0 0 0 -1 0 0;
estimate 'time 6' therapy*time 0 0 1 0 0 0 -1 0;
estimate 'time 12' therapy*time 0 0 0 1 0 0 0 -1;
ods output SolutionF=sfm.solution_ccmv; ods output CovB=sfm.covb_ccmv;
ods output covparms=sfm.covparm_ccmv; ods output estimates=sfm.estimate_ccmv;
ods output asycov=sfm.asycov_ccmv; run;

proc mianalyze parms=sfm.solution_ccmv edf=180 covb(effectvar=rowcol)=sfm.covb_ccmv;
class therapy time; modeleffects therapy*time; run;

data sfm.estimate_ccmv; set sfm.estimate_ccmv;
if Label='time 0' then effect='t1'; if Label='time 1' then effect='t2';
if Label='time 6' then effect='t3'; if Label='time 12' then effect='t4';
proc mianalyze parms=sfm.estimate_ccmv edf=180; modeleffects t1 t2 t3 t4; run;

```

```
proc mi data=sfm.sfm_mono seed=123 out=sfm.sfm_ncmv simple nimpute=1 maximum=100;
class therapy; var therapy sfm0 sfm1 sfm6 sfm12;
monotone reg; mmar model(sfm6 sfm12 / modelobs=ncmv); run;
```

```
proc mixed data=sfm.sfm_ncmv_long method=ml asycov;
class therapy id_no time; by _imputation_;
model sfm = therapy*time / noint s residual cl covb ddfm=sat;
repeated time / subject=id_no type=un r rcorr;
estimate 'time 0' therapy*time 1 0 0 0 -1 0 0 0;
estimate 'time 1' therapy*time 0 1 0 0 0 -1 0 0;
estimate 'time 6' therapy*time 0 0 1 0 0 0 -1 0;
estimate 'time 12' therapy*time 0 0 0 1 0 0 0 -1;
ods output SolutionF=sfm.solution_ncmv; ods output CovB=sfm.covb_ncmv;
ods output covparms=sfm.covparm_ncmv; ods output estimates=sfm.estimate_ncmv;
ods output asycov=sfm.asycov_ncmv; run;
```

```
proc mianalyze parms=sfm.solution_ncmv edf=180 covb(effectvar=rowcol)=sfm.covb_ncmv;
class therapy time; modeleffects therapy*time; run;
```

```
data sfm.estimate_ncmv; set sfm.estimate_ncmv;
if Label='time 0' then effect='t1'; if Label='time 1' then effect='t2';
if Label='time 6' then effect='t3'; if Label='time 12' then effect='t4';
proc mianalyze parms=sfm.estimate_ncmv edf=180; modeleffects t1 t2 t3 t4; run;
```

PCS score from SF-12

```
proc mixed data=sfp.sf_phy method=ml; class therapy id_no time;
model sf12_physical = therapy*time / noint s residual cl ddfm=sat outpm=sfp.predict;
repeated time / subject=id_no type=un r rcorr;
estimate 'time 0' therapy*time 1 0 0 0 -1 0 0 0;
estimate 'time 1' therapy*time 0 1 0 0 0 -1 0 0;
estimate 'time 6' therapy*time 0 0 1 0 0 0 -1 0;
estimate 'time 12' therapy*time 0 0 0 1 0 0 0 -1; run;
```

```
proc mi data=sfp.sfp_wide seed=123 out=sfp.sfp_mono simple maximum=100;
var therapy sfp0 sfp1 sfp6 sfp12; mcmc impute=monotone; run;
```

```
proc mi data=sfp.sfp_mono seed=123 out=sfp.sfp_ccmv simple nimpute=1 maximum=100;
class therapy; var therapy sfp0 sfp1 sfp6 sfp12;
monotone reg; mmar model(sfp6 sfp12 / modelobs=ccmv); run;
```

```
proc mixed data=sfp.sfp_ccmv_long method=ml asycov;
class therapy id_no time; by _imputation_;
model sfp = therapy*time / noint s residual cl covb ddfm=sat;
repeated time / subject=id_no type=un r rcorr;
estimate 'time 0' therapy*time 1 0 0 0 -1 0 0 0;
estimate 'time 1' therapy*time 0 1 0 0 0 -1 0 0;
estimate 'time 6' therapy*time 0 0 1 0 0 0 -1 0;
estimate 'time 12' therapy*time 0 0 0 1 0 0 0 -1;
ods output SolutionF=sfp.solution_ccmv; ods output CovB=sfp.covb_ccmv;
ods output covparms=sfp.covparm_ccmv; ods output estimates=sfp.estimate_ccmv;
ods output asycov=sfp.asycov_ccmv; run;
```

```
proc mianalyze parms=sfp.solution_ccmv edf=180 covb(effectvar=rowcol)=sfp.covb_ccmv;
class therapy time; modeleffects therapy*time; run;
```

```
data sfp.estimate_ccmv; set sfp.estimate_ccmv;
if Label='time 0' then effect='t1'; if Label='time 1' then effect='t2';
if Label='time 6' then effect='t3'; if Label='time 12' then effect='t4';
proc mianalyze parms=sfp.estimate_ccmv edf=180; modeleffects t1 t2 t3 t4; run;
```

```
proc mi data=sfp.sfp_mono seed=123 out=sfp.sfp_ncmv simple nimpute=1 maximum=100;
class therapy; var therapy sfp0 sfp1 sfp6 sfp12;
```

```

monotone reg; mmar model(sfp6 sfp12 / modelobs=ncmv); run;

proc mixed data=sfp.sfp_ncmv_long method=ml asycov;
class therapy id_no time; by _imputation_;
model sfp = therapy*time / noint s residual cl covb ddfm=sat;
repeated time / subject=id_no type=un r rcorr;
estimate 'time 0' therapy*time 1 0 0 0 -1 0 0 0;
estimate 'time 1' therapy*time 0 1 0 0 0 -1 0 0;
estimate 'time 6' therapy*time 0 0 1 0 0 0 -1 0;
estimate 'time 12' therapy*time 0 0 0 1 0 0 0 -1;
ods output SolutionF=sfp.solution_ncmv; ods output CovB=sfp.covb_ncmv;
ods output covparms=sfp.covparm_ncmv; ods output estimates=sfp.estimate_ncmv;
ods output asycov=sfp.asycov_ncmv; run;

proc mianalyze parms=sfp.solution_ncmv edf=180 covb(effectvar=rowcol)=sfp.covb_ncmv;
class therapy time; modeleffects therapy*time; run;

data sfp.estimate_ncmv; set sfp.estimate_ncmv;
if Label='time 0' then effect='t1'; if Label='time 1' then effect='t2';
if Label='time 6' then effect='t3'; if Label='time 12' then effect='t4';
proc mianalyze parms=sfp.estimate_ncmv edf=180; modeleffects t1 t2 t3 t4; run;

```

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Richting: **Master of Statistics-Biostatistics**

Jaar: **2018**

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**Ong, Fenny**

Datum: **15/06/2018**