Workplace Portfolio

Submitted in accordance the requirements for the
Masters of Biostatistics
(Biostatistics Collaboration of Australia)

An assessment and evaluation of alternative methods for modeling lymphedema in the SNAC trial.

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Glossary of terms

AC	Axillary clearance
AIC	Akaike information criterion, a model fit statistic which penalizes for the number of dependent variable in a regression model, for a given data set the model with the minimum AIC value offer the best fit.
Bias	Is the difference between an estimator's expected value and its true value.
Contralateral	Denoting the upper limb opposite to which the condition of interest occurs; i.e. in the SNAC trial contralateral specifically refers to the non-surgery arm.
CiV_{con}	Change in volume from baseline at 5 years (unless noted otherwise) in the ipsilateral limb
CiV_{ips}	Change in volume from baseline at 5 years (unless noted otherwise) in the contralateral limb
δCiV	Difference between the CiV_{ips} and CiV_{contra}
δPCV_b	The difference in PCV_b between the ipsilateral and contralateral limb
i.i.d.	Independent and identically distributed
Ipsilateral	Side of the body where the condition of interest – i.e. tumor cells - have been detected. For example, in the SNAC trial ipsilateral limb refers to the surgery limb.
ITT	Intention to treat means all patients enrolled and randomly allocated to treatment are included in the analysis and analysed as per the treatment group they were randomised too.
MSE	Mean squared error of an estimator is the average of the squares of the difference between the estimator and what is estimated.
R^2	R-squared or r^2, in a regression model R^2 indicates the proportion of the variance in the dependent variable that is explained by the

	independent variables.
Adj. R^2	Adjusted R^2 is the R^2 penalized for the number of dependent variable in a regression model.
RAC	Routine axillary clearance
RCT	Randomised controlled trial
Rho	The estimated correlation.
r.v.'s	Random variables
SNAC	Sentinel Node versus Axillary Clearance trial
SNBM	Sentinel node biopsy management
SNB	Sentinel node biopsy
SSSS	SNAC study specific scales
V_{ips}	Volume in the ipsilateral limb at 5 years

Preface

Students Role

Over the last 3 years I have had involvement to a greater or lesser extent with the analysis of the 5 years results for the Sentinel Node versus Axillary Clearance (SNAC) trial - The Royal Australasian College of Surgeon's multicentre randomized controlled trial (RCT) comparing sentinel node biopsy management (SNBM) versus routine axillary clearance (RAC) in women with clinically node-negative early onset breast cancer. In particular over the last year I have collaborated with the principal investigator to prepare the analysis for SNAC 5 year results and manuscript which has subsequently been published in a peer reviewed clinical journal.

The pre-specified primary outcome for the SNAC trial was percentage increases in arm volume from baseline (PCV_b) in the ipsilateral arm (i.e. the arm receiving the surgery). The potential exists that a proportion of this change in limb volume would be associated with confounding factors such as weight and muscle change over time.

A novel approach to model the arm swelling which accounts for these potential confounding factors and accommodates the differential growth between the arms included the contralateral arm (the opposite arm to that receiving surgery) data in the assessment of lymphedema. Arm swelling was calculated as PCV_b in both the ipsilateral and contralateral arm for the 1088 women from the SNAC trial. The difference in PCV_b between the ipsilateral and contralateral arm (δPCV_b) was calculated and assumed to be a measure of swelling accounting for confounders, differential growth between the arms and other factors (weight gain/loss etc). Analysis of the 5 year data included δPCV_b as the dependent variable.

The purpose of this work place project was to build on prior work and explore the assumption that the contralateral limb data afforded improvements in modeling

lymphedema (arm swelling) and thus allow for a more efficient estimate of the treatment effect.

Of interest was how the assessment of the efficiency of the various models of interest was conducted. The efficiency of the various models was estimated via a simulation experiment. The results of the simulation experiment suggest that a closer model fit (improved efficiency) is garnered via use of both the ipsilateral and contralateral arms in the assessment of lymphedema. This finding was corroborated in the SNAC trial when comparing models with and without the contralateral limb data.

Reflections on learning

As important or significant as this finding is, I believe that it is in the implementation of the scientific method where I have gained the most over the course of the work place project (WPP). The scientific method implies: a) asking a question i.e. 'which of various pre-specified regression models, best models the variability associated with the measurement of lymphedema and thus affords the most efficient estimate of the treatment effect'; b) designing and running a simulation experiment to assess the efficiency of the regression models; c) implementation of the regression model identified in the simulation experiment on the SNAC trial data.

The approach of performing a simulation experiment to ascertain which method to pursue in subsequent analysis is one I envisage I will use again. In terms of the practicalities of running a simulation experiment, I had no experience of generating multivariate normal data previously. Any deficiency here was satisfied by SAS documentation courtesy of Wicklin (2013).

Other than the data simulation, I am familiar with the statistical principles and methods implemented in the report. Least squares regression analysis was performed looking at the treatment effect at 5 years. Models were unadjusted and adjusted for various variables.

All statistical analyses (other than graphs) were performed using SAS, version 9.3. Graphs were produced in STATA v12.

Teamwork

The project was self-guided; no teamwork was required other than regular meetings with my supervisor.

Ethical considerations

A request to the RACS group was made to use the SNAC data for the purpose of conducting a sub-study with the intention to submit to as a WPP. Approval for use of the data was formally given at the SNAC trials operations executive committee meeting on the 11th of October 2016.

The completed report was forwarded to the principal investigator of the SNAC trial as a matter of courtesy.

De-identified data was used for all analysis for the WPP.

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Project Report

Title

An assessment and evaluation of alternative methods of modeling lymphedema in the SNAC trial.

Location Dates

The project was conducted at the NHMRC CTC over semester 2 2016.

Context

Between 15% and 20% of breast cancer patients develop lymphedema following breast cancer surgery (Petrek et al 2000). Detection of lymphedema - as with the SNAC trial - often involves taking the ipsilateral arm volume measurements at baseline and then intermittently post-operatively. An issue with restricting the assessment of lymphedema to the ipsilateral arm is that the potential exists for a proportion of this change in limb volume to be associated with confounding factors such as weight and muscle change over time.

The assumption underlying this work place project is that information afforded by the contralateral arm would account for some of the potential confounding factors. The purpose of this report then is to assess the impact of inclusion of the contralateral arm data on SNAC trial analysis results and to further interrogate the efficiency gains afforded by the contralateral arm volume. A simulation experiment was conducted to evaluate the efficiency of different estimators. The analysis model which gave the most efficient estimate was used to analyse the SNAC trial data. This methodology (the simulation experiment) was used, as opposed to performing all possible analyses then choosing that which best suits an investigators perception.

Student contribution

Research was undertaken into various aspects of this WPP including that which informed an understanding of the issues relating to the detection of lymphedema, simulation of multivariate normal distributions, detecting collinearity via eigenvalue decomposition and bootstrapping. The latter three methods (simulation, collinearity and bootstrapping) were not previously encountered in the Bio-statistics Collaboration of Australia.

Statistical issues

Statistical issues addressed in this WPP include 1) simulation experiment, 2) Least squares regression analysis, 3) Model selection and 4) Assessment of collinearity in final regression model.

Declaration

I David Espinoza certify that this project is evidence of my own work, with direction and assistance provided by my project supervisor. Further this work has not been previously submitted for academic credit.

20/06/2017

David Espinoza Date

Supervisor Statement

David has worked independently this semester to complete the report for this workplace project. Several meetings throughout the semester occurred where David has shown good progress with the development of ideas and statistical methods and in the communication of methods and results.

20/06/2017

Val Gebski Date

Project Description

Background

Lymph nodes are organs which form part of the body's lymphatic system. The lymph nodes play an active role in the immune system but also help determine if cancer cells have developed and spread throughout the body. Breast cancer spreads through the lymphatic system to lymph nodes close to the cancer site, in most likely for breast cancer to the lymph nodes located in the axilla, or armpit area.

The use of axillary clearance (AC) - removal of lymph nodes from the arm pit - for the detection of tumor cells carries the potential for risks and complications including but not limited to lymphedema. Lymphedema is long term severe arm swelling caused by damage to the lymphatic system. An interruption or blockage in the lymphatic system causes lymph fluid to build up in subcutaneous tissue in the arm. Women with lymphedema resulting from 'breast cancer therapy can experience a substantial degree of functional impairment and psychological morbidity and diminished quality of life' (Erickson 2001: 96).

The first lymph node which cancer cells are most likely to spread is defined as the sentinel lymph node. Sentinel-lymph-node biopsy management (SNBM) is a procedure where the identified sentinel node is removed and examined for the presence of cancer cells. The results of the biopsy guide the management of the cancer. In general SNBM avoids the use of an AC in the cases where no metastasis has been detected in the sentinel node thus minimising side effects and morbidity with a more invasive procedure.

The Royal Australasian College of Surgeon's Sentinel Node versus Axillary Clearance (SNAC) trial is a multicentre randomised controlled trial (RCT) comparing sentinel node biopsy management (SNBM) versus routine axillary clearance (RAC) in women with

clinically node-negative early onset breast cancer. 544 women were randomised to RAC (sentinel lymph-node biopsy followed by immediate AC) while 544 women were randomised to SNBM (sentinel lymph-node biopsy followed by an AC if the sentinel lymph-node was deemed positive or if the sentinel lymph-node could not be detected). Women assigned to SNBM which returned positive cancer results from the histopathology were required to return for an AC at a later date.

The objective of the SNAC trial was to determine if sentinel node biopsy (and axillary clearance in node positive patients) resulted in less morbidity compared to RAC.

Quantitative measures collected by the SNAC trial included evaluations of shoulder function, arm volume for both the ipsilateral and contralateral arms and patients' arm morbidity self-assessed via a SNAC Study Specific Scale quality of life questionnaire.

Arm volume was estimated using the formula for a truncated cone

$$V = \frac{100}{12\pi}\left(C_a^2 + C_b^2 + C_a^2 * C_b^2\right)$$

where C_a and C_b are the apex and base circumference of the cone. Each cone was defined as the arm circumference measured at 10cm intervals commencing from the tip of the middle finger and proceeding upwards along the arm. The total volume for each arm is obtained by summing the volumes of 5 truncated cones.

Assessments were carried out at baseline, 6months, 12 months and then yearly until 5 years.

The SNAC pre-specified primary outcome was percentage increases in arm volume from baseline (PCV_b) in the ipsilateral arm (Gill et al, 2009). Secondary endpoints were the proportion of women with an increase in PCV_b of greater than 15% and changes in SNAC study specific scales (SSSS) score from baseline. The cut-point of 15% was assumed to indicate the presence of lymphedema.

The potential exists that a proportion of the PCV_b to be associated with confounding factors such as weight and muscle change over time. Various methods have been suggested to tease out the impact of these factors in the measurement of lymphedema and thus enable assessment of the treatment effect which is more representative. There is no agreed method for the detection of arm swelling (Petrek et al, 2000).

Aim

The assumption underlying this work place project is that information afforded by the contralateral arm would account for some of the potential confounding factors associated with lymphedema. The broad research objective of the work place project was then to determine how inclusion of the contralateral arm data in the assessment of lymphedema would impact the analysis results in the SNAC trial.

The proposed work place project was broken up into two parts.

Part 1: Simulation Study

A simulation experiment was conducted to evaluate the efficiency of 6 pre-specified regression models designed to model lymphedema. The primary hypothesis of the simulation experiment was that inclusion of the contralateral arm volume in regression models will improve the efficiency of the estimate of the treatment effect.

Recall that the objective of the SNAC trial was to determine if treatment, SNBM compared to RAC resulted in reduced arm swelling and thus less morbidity. An efficient (stable, consistent) estimate of lymphedema would thus afford a more precise estimate of the effect of treatment on lymphedema in the SNAC trial.

Part 2: Analysis of lymphedema in SNAC study

Using the most efficient analysis method identified by the simulation experiment in part 1 of the work place project the treatment effect on lymphedema was estimated in the

SNAC trial. Additionally an assessment of the gain in information afforded by inclusion of the contralateral limb data was conducted.

Methods

Part 1: simulation study.

Development of a population model:

Descriptive analysis of the SNAC ipsilateral and contralateral arm volumes was undertaken. The analysis was conducted by treatment groups SNBM and RAC for both the intention to treat cohort and for the subgroup of women with a negative SNB at baseline.

The ipsilateral and contralateral arm volumes at baseline and at 5 years were summarised as mean and variance. Covariance between arm volume (ipsilateral and contralateral) over baseline and 5 years were presented. The degree of relationship between and within arm volumes and over time was assessed via Pearson correlation. Confidence intervals for the correlation coefficient were estimated via use of Fisher's z-transformation and via the percentile bootstrapped method.

Mean arm volume over time for the ipsilateral and contralateral limb were graphed by allocated treatment for both the intention to treat cohort and for women with a negative SNB at baseline. A histogram was used to depict the distribution of the ipsilateral and contralateral arm volume at baseline.

A population model for arm volume changes associated with breast cancer surgery was developed guided by descriptive analysis of the SNAC trial data. Hypothesized factors affecting arm volume over time were:

- general changes in weight and muscle
- allocated treatment group
- baseline SNB status

Based on the descriptive analysis the simulated data used in the simulation experiment was generated as a multivariate normal.

Recall that women randomised to the SNBM group which had a positive SNB or if the sentinel node could not be detected had a subsequent AC. To replicate the design of the SNAC trial if subject 'i' was allocated to the RAC group or if they were randomly selected (with probability π) as having a positive SNB at baseline, then the population parameters (mean vector and covariance matrix) were given by those of the RAC group.

Simulating normal distributions

The multivariate normal data was generated via the SAS RANDNORMAL function. The RANDNORMAL function generates random multivariate normal distributions by transforming independent and identically distributed (i.i.d.) standard normal random variables (r.v.'s).

To generate independent standard normal r.v.'s the Box-Muller method is used; i.e. if U_1 and U_2 are i.i.d. uniform(0,1) random variables then

$$Z_1 = \cos\left(2\pi U_2\right)\log\left(\frac{1}{U_1}\right)^{1/2}$$

$$Z_2 = \sin\left(2\pi U_2\right)\log\left(\frac{1}{U_1}\right)^{1/2}$$

are i.i.d N(0,1). A d-dimensional multivariate normal with mean vector μ and covariance matrix Σ is generated by first generating i.i.d standard normals say $z=(z_1, z_2, z_3, \ldots, z_d)$, then the transformation of the i.i.d standard normals $X = T^T z + \mu$ is distributed as a $N_d(\mu, \Sigma)$ (Gentle, 2003). The element T is such that $T^T T = \Sigma$ i.e. the Cholesky decomposition of the covariance matrix Σ.

Regression models and the simulation experiment

Regression Models to be assessed are:

- Ipsilateral arm volume (V_{ips}) at 5 years adjusted for treatment,
- V_{ips} adjusted for treatment and baseline ipsilateral arm volume,
- Changes in arm volume between baseline and 5yrs in the ipsilateral arm (CiV_{ips}) adjusted for treatment,
- CiV_{ips} adjusted for treatment & baseline volume in the ipsilateral arm;
- CiV_{ips} adjusted for treatment & change in volume in the contralateral arm (CiV_{con}),
- Difference in the CiV between the ipsilateral and contralateral arm (δCiV) adjusted for treatment.

A simulation experiment of 1000 simulations of the SNAC data of sample size N=1000 was conducted to determine which of the 6 prespecified models would best account for the inherent variability in the data and, thus afford an efficient estimate of the treatment effect.

For the various models considered Least squares regression analysis was conducted to estimate the mean treatment effect; bias the difference between an estimator's expected value and its true value; mean square error (MSE) the average of the squares of the difference between the estimator and what is estimated; Akaike information criterion (AIC) a relative measure of goodness of fit which penalizes for number of dependent variables (for the given dataset the preferred model is one with the minimum AIC value); R^2 which measures the proportion of the variance in the dependent variable and the adjusted R^2 which includes a penalty for the number of dependent.

The MSE is the primary measure of efficiency used to compare the 6 prespecified models. Note that the MSE can also be obtained as the sum of the variance of an estimator plus the square of its bias. The MSE then has two components, one a measure of the precision/variability of the estimator and the other a measure of the accuracy/bias of the estimator. The model then with minimum MSE was deemed to offer the most efficient estimate while controlling for bias.

The simulation experiment was further conducted under several scenarios to assess their impact on the prespecified models. Scenarios investigated: 1) when there is no treatment effect (none, some and substantial), 2) changing the proportion with positive SNB at baseline, 3) changing the randomisation allocation ratio (1:1 and 2:1) and, 4) changing the correlation between the variables.

Under the assumption that the arm volumes are normally distributed and noting that differences of normal random variables are normal it follows that CiV and δCiV are normal. Lumley et al (2002) show that in public health research regression parameters for t-test and least-squares linear regression are valid for modest sample sizes where modest is often fewer than 100. The simulated data and the SNAC data population size was ~1000 thus the normality of the residuals of the proposed simple and multivariate linear regression models was assumed.

The simulated treatment effect

Turning our attention to model 1, a regression model for V_{ips} at 5 years adjusted for treatment can be written as

$$V_{ips} = \beta_0 + \beta_1 X_t + \epsilon$$

where V_{ips} is a n*1 vector of the ipsilateral arm volumes at 5 years, β_0 and β_1 are the regression coefficients which are to be estimated, X_t is a n*1 vector of 1's and 0's designating the allocated treatment arm (1=SNBM and 0=RAC) and lastly ϵ is a n*1 vector of standard normally errors.

Taking expectation of both sides of the regression equation above and setting X_t to be equal to '1' or '0' we have

$$E(V_{ips} | X_t = 1) = \beta_0 + \beta_1$$

and

$$E(V_{ips} | X_t = 0) = \beta_0$$

Subtracting the second equation from the first gives β_1, the regression coefficient for the treatment effect

$$\beta_1 = E(V_{ips}|X_t=1) - E(V_{ips}|X_t=0)$$

Recall that the mean vector and covariance matrix for the SNBM group was randomly given with probability π by that of the RAC group if they were designated as having a positive SNB at baseline. By taking the sum of the expectation of ipsilateral arm volume in the SNBM group (i.e. V_{ips} given X_t=1) over the disjoint union of the events, SNB positive (S_n=1) and SNB negative (S_n=0); the expected 5 year volume for the ipsilateral limb in the SNBM group is then

$$\begin{aligned}
&E(V_{ips}|X_t=1)\\
&= E(V_{ips}|X_t=1,\, S_n=1)\, P(S_n=1) + E(V_{ips}|X_t=1,\, S_n=0)\, P(S_n=0)\\
&= E(V_{ips}|X_t=1,\, S_n=1)\, \pi + E(V_{ips}|X_t=1,\, S_n=0)\,(1-\pi)
\end{aligned}$$

Thus for β_1, the treatment effect we have

$$\begin{aligned}
&E(V_{ips}|X_t=1) - E(V_{ips}|X_t=0)\\
&= E(V_{ips}|X_t=1,\, S_n=1)\, \pi + E(V_{ips}|X_t=1,\, S_n=0)\,(1-\pi) - E(V_{ips}|X_t=0)\\
&= E(V_{ips}|X_t=1,\, S_n=0)\,(1-\pi) - E(V_{ips}|X_t=0) + E(V_{ips}|X_t=1,\, S_n=1)\, \pi
\end{aligned}$$

Now as the 5 year arm volume in the SNBM group given a positive SNB is the same as that of the RAC group, we have

$$E(V_{ips}|X_t=1,\, S_n=1) = E(V_{ips}|X_t=0)$$

the regression coefficient for the treatment effect β_1 reduces to

$$\begin{aligned}
&E(V_{ips}|X_t=1,\, S_n=0)\,(1-\pi) - E(V_{ips}|X_t=0)\,(1-\pi)\\
&= \left[\, E(V_{ips}|X_t=1,\, S_n=0) - E(V_{ips}|X_t=0)\right](1-\pi)
\end{aligned}$$

That is, the true treatment effect is weighted by the probability of a negative sentinel node (1-π). Denote the difference in the 5 year ipsilateral arm volume between the RAC group and the SNBM group given a negative SNB as μ, then we have $\beta_1 = \mu\,(1-\pi)$.

Similarly derivation of the treatment effect for the 6 pre-specified models gives the treatment effect as $\beta_1 = \mu (1-\pi)$ (see appendix for details).

Part 2: Analysis of lymphedema in SNAC study

The treatment effect on lymphedema was estimated in the SNAC trial using the most efficient regression model identified by the simulation experiment conducted in part 1 of this project. Descriptive statistics of baseline potential risk factors which may influence arm volumes presented, mean (SD) for continuous factors and N (%) for categorical variables. Univariate least squares regression analysis was conducted to identify potential risk factors of lymphedema. A multivariate model was developed based on backwards selection procedure. For the purpose of model selection, potential risk factors found to be univariately associated with lymphedema at or below a p-value of 0.2 were included in the full risk set. The conservative level of 0.2 was used to ensure no important factors were excluded from the full analysis risk set. Backwards selection was conducted on the full risk set to identify the parsimonious model.

The treatment effect was assessed univariately and when adjusted. The MSE, AIC and adj. R^2 were used to assess the efficiency gains in the estimate of the treatment effect that the contralateral limb data affords.

Data Management

The first and last randomisation for the SNAC study occurred in May 2001 and May 2006. The SNAC one year and 3 year trial results (Wetzig 2015) have previously been published. The 5 year results have been reported and submitted to a journal for publication. Analysis for the WPP used data from the SNAC trial which has been previously analysed. As such the required data cleaning/manipulation for the purpose of this WPP was omitted.

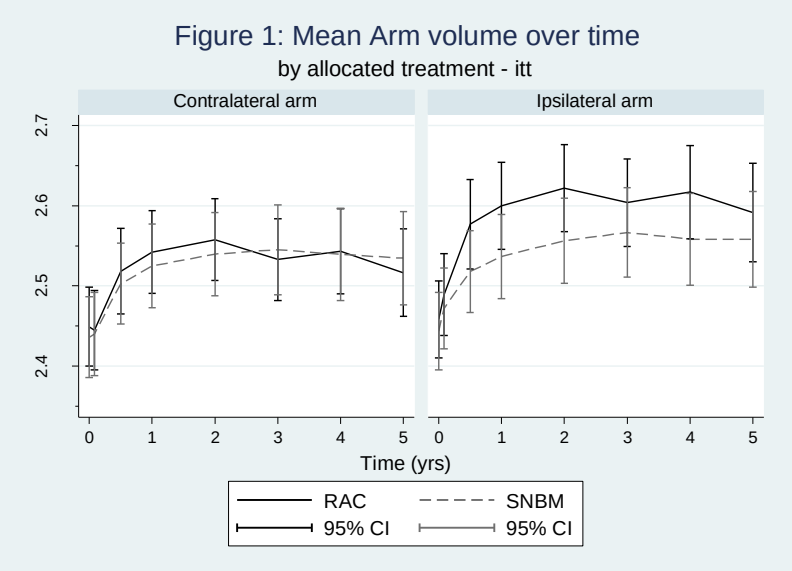
In the WPP the issues of missing data where not addressed. This project focuses on the impact of different sources of information (contralateral limb data) on potential analysis results.

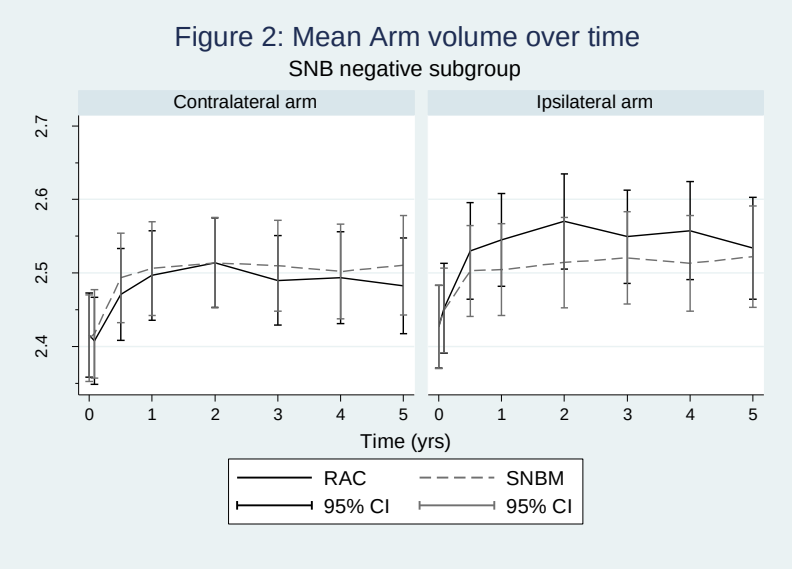
Results

Part 1: simulation study.

Descriptive analysis of the SNAC data

Figures 1 and 2 depict arm volume in the ipsilateral and contralateral arms over time (i.e. at baseline, 1, 6 and 12 months then yearly until 5 years) for both the intention to treat (ITT) population and the sentinel node biopsy (SNB) negative subgroup.





Arm volume for the SNAC ITT cohort increases from baseline in both the ipsilateral and contralateral limbs and was sustained for the duration of the trial (Figure 1). Over time there appears to be little or no difference in the contralateral limb volume between the allocated treatment groups. The ipsilateral arm volume was greater in magnitude in the RAC group compared to the SNBM group for the duration of the trial.

Table 1: SNAC Baseline sentinel node biopsy status

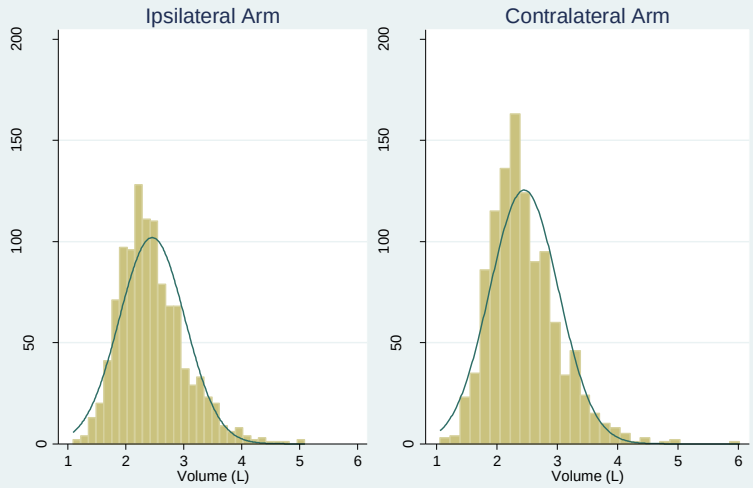
	N	+ve	-ve
RAC	531	168	363
SNBM	538	182	356
total	1069	350	719

The distribution of SNB status at baseline is given in Table 1. At baseline, 34% (182/538) of the SNBM group were found to have a positive SNB. As specified in the protocol these women had an immediate AC. The arm volume over time for patients that have a negative SNB at baseline (Figure 2) show similar arm patterns as that for the ITT cohort (Figure 1), though the magnitude of the arm volume increase was smaller in both the ipsilateral and contralateral limb.

Distribution of arm volumes at baseline in the SNAC study

The distribution of the arm volume in both the contralateral and ipsilateral arms at baseline is represented in Figure 3. The histograms of arm volumes at baseline have a symmetric distribution. The overlaid normal density curves suggest that arm volumes at baseline are normally distributed. SNAC baseline arm volume mean (standard deviation) for the ipsilateral arm is 2.45L (0.57L) while that of the contralateral arm is 2.45L (0.57L). Arm volumes for both the ipsilateral and contralateral arms are normally distributed with mean 2.45L and standard deviation 0.57L.

Figure 3: Histogram arm volume at baseline



The Pearson correlation 'between' the ipsilateral and contralateral arms at baseline and at 5 years is given in Table 2. As expected the SNAC data show a high level of correlation between an individual's ipsilateral and contralateral arm volume at both baseline and at 5 years (0.98 and 0.95 respectively).Similarly the correlation 'within' the ipsilateral and 'within' the contralateral arms between baseline and 5 year show a high level of correlation (0.88 and 0.87 respectively). Confidence intervals for the correlation coefficient where estimated via use of Fisher's z-transformation and via the percentile bootstrapped method. Both estimates agree.

Table 2: SNAC arm volume correlation and 95% CI

	Rho	95% CI's
Ipsilateral and Contralateral limb (between)		
Baseline	0.98	(0.97 ,0.98)
5 year	0.95	(0.95 ,0.96)
Baseline and 5 year (within)		
Contralateral	0.88	(0.87 ,0.90)
Ipsilateral	0.87	(0.85 ,0.89)

Note:

1. Ipsilateral and contralateral arm volume Pearson correlations presented.
2. The 95% CI presented where calculated via: a. Fisher's z-transformation, b. percentile bootstrapped method. Note these CI concur to 2 decimal places.
3. The bootstrapped 95% CI based on 1000 repeated samples of the data; sampling with replacement was conducted.

4. Rho is the estimated correlation.

The mean vector and covariance matrix for arm volumes for the SNAC data is given in Table 3 for both the ITT population and the SNB positive and negative subgroups. Both the ITT population and the SNB status subgroups mean arm volumes increase in the respective arms over the course of the study (baseline to 5 years). As previously observed the magnitude of the increase in arm volume is smallest within the SNB negative subgroup while the largest change occurs for the SNB positive subgroup.

Table 3: SNAC Mean vector and covariance matrix of arm volumes at baseline and 5 years, By allocated treatment – ITT population

	RAC					SNBM				
		Cov: baseline		Cov: year 5			Cov: baseline		Cov: year 5	
	mean	Ipsi.	Cont.	Ipsi.	Cont.	mean	Ipsi.	Cont.	Ipsi.	Cont.
Ipsilateral baseline	2.46	0.32				2.44	0.32			
Contralateral baseline	2.45	0.31	0.33			2.44	0.32	0.35		
Ipsilateral year 5	2.59	0.29	0.28	0.41		2.56	0.30	0.29	0.38	
Contralateral years 5	2.52	0.26	0.26	0.34	0.32	2.53	0.29	0.29	0.36	0.36
By SNB status at baseline										
	SNB positive					SNB negative				
		Cov: baseline		Rho: year 5			Cov: baseline		Cov: year 5	
	mean	Ipsi.	Cont.	Ipsi.	Cont.	mean	Ipsi.	Cont.	Ipsi.	Cont.
Ipsilateral baseline	2.50	0.37				2.43	0.30			
Contralateral baseline	2.50	0.37	0.39			2.41	0.29	0.32		
Ipsilateral year 5	2.68	0.32	0.31	0.47		2.53	0.28	0.27	0.35	
Contralateral years 5	2.59	0.29	0.29	0.39	0.37	2.50	0.26	0.26	0.26	0.37

Note:

1. Ipsi. and Cont. refer to ipsilateral and contralateral respectively.
2. Cov denotes covariance.

Population model, the simulated multivariate normal parameters:

Baseline and 5 year ipsilateral and contralateral arm volumes were simulated as multivariate normal where mean vectors and covariance matrices were defined for the simulated treatment groups - RAC and SNBM group - as follows:

Table 4: Simulated multivariate mean vector and covariance matrix

	RAC		SNBM	
	Cov.: baseline	Rho: year 5	Cov.: baseline	Rho: year 5

	mean	Ipsi.	Cont.	Ipsi.	Cont.	mean	Ipsi.	Cont.	Ipsi.	Cont.
Ipsilateral baseline	2.45	0.32				2.45	0.32			
Contralateral baseline	2.45	0.31	0.33			2.45	0.32	0.35		
Ipsilateral year 5	2.59	0.29	0.28	0.41		2.56	0.30	0.29	0.38	
Contralateral years 5	2.53	0.26	0.26	0.34	0.32	2.53	0.29	0.29	0.36	0.36

Note:

1. Ipsi. and Cont. refer to ipsilateral and contralateral respectively.
2. Cov. denotes covariance.
3. If subject 'i' was allocated to the RAC group or if they were randomly selected (with probability π=0.3) as having a positive SNB at baseline, then the mean vector and covariance matrix were given by those of the RAC group.

The simulation experiment

The average estimated treatment effect, bias, adjusted R^2, MSE and AIC for the various models of interest are presented in Table 5. Model 2 and 5 have the highest adjusted R^2 of 0.688 and 0.678 respectively indicating that ~32% of the variability in the dependent variable (V_{ips} or CiV_{ips}) is unaccounted for, in either model. Compared to the other models an adjusted R^2 of .678 represents a 38 (=0.678/0.018) fold improvement over the next highest adjusted R^2 value of 0.018 (model 4). Model 5 has the smallest MSE (0.040) followed closely by model 6 (0.045). Model 5 offers a .3 to .1 fold improvement in MSE over models 1 to 4. The treatment estimated effect (β_{treat}) concurs with the true treatment (μ) to 3 decimal places for models 2 to 6. The estimated bias, the difference between the estimated treatment (β_{treat}) and true treatment (μ) offer little to differentiate the models. Model 5 has the smallest AIC; indicating that for the simulated data, on average model 5 - relative to the other models - offers the best fit while still accounting for number of covariates in the model.

Table 5: Model fit statistics

Model	β_{treat} (SD)	bias	MSE	Adj. R^2	AIC	Model description
1	-0.029 (0.040)	-0.000	0.395	0.001	-929	V_{ips} adjusted for treatment
2	-0.030 (0.022)	-0.001	0.123	0.688	-2094	Model 1 + baseline ipsi. arm volume
3	-0.030 (0.022)	-0.001	0.125	0.002	-2079	CiV_{ips} adjusted for treatment
4	-0.030 (0.022)	-0.001	0.123	0.018	-2094	Model 3 + baseline ipsi. arm volume
5	-0.030 (0.013)	-0.001	0.040	0.678	-3212	Model 3 + CiV_{con}
6	-0.030 (0.014)	-0.001	0.045	0.005	-3100	δCiV adjusted for treatment

Note:

1. *Model parameters: μ=-0.03, π=0.3, 1:1 Treatment allocation.*
2. *Fit statistics based on 1000 simulations of data (sample size 1000).*

In general under the various scenarios conducted (μ ϵ [-0.06, -0.03, 0.00], π ϵ [0.1, 0.3, 0.5], and 1:1 or 2:1 Treatment allocation, refer to appendix Table 11) model 5 accounts for more variability in the dependent variable than the other models (maximises R^2), has the lowest MSE thus offering the most efficient estimate of the treatment effect while controlling for bias and further offers the best fit (smallest AIC).

Summary for the simulation experiment

Based on the MSE, model 5 (CiV in the ipsilateral arm at 5 years adjusted for treatment and CiV in the contralateral arm) was deemed to offer the most efficient estimate of the treatment effect and further offered the best fit and thus selected for all subsequent analysis.

Part 2: Analysis of lymphedema in SNAC study

Baseline factors (descriptive statistics)

Baseline descriptive statistics of potential factors which may influence arm volumes is given in Table 6. Other than the variable '15+ nodes removed in AC and SNB' all other prognostic factors are well balanced between the allocated treatment groups (SNBM and RAC). Balance was not expected in the variable '15+ nodes removed in AC and SNB' as fewer node samples were expected in the SNBM group.

Table 6: SNAC Baseline descriptive statistics

Factors	Level	SNBM (N=544)	RAC (N=544)
CiV contralateral arm: mean(SD)		0.06 (0.27)	0.06 (0.28)
WHO Performance Status	1	32 (6%)	25 (5%)
Tumour Palpable	Yes	309 (57%)	309 (57%)
Other major concurrent illness	Yes	238 (44%)	228 (42%)
Diabetes	Yes	33 (6%)	31 (6%)

Factors	Level	SNBM (N=544)	RAC (N=544)
Hypertension	Yes	123 (23%)	111 (21%)
Other illness (not diab. or hyper.)	Yes	154 (29%)	158 (29%)
Age: mean(SD)		57.9 (10.3)	58.3 (10.1)
Age 50+	Yes	425 (78%)	424 (78%)
Weight: mean(SD)		73.2 (16.1)	72.9 (15.0)
Height: mean(SD)		161.8 (6.8)	162.0 (6.8)
BMI: mean(SD)		27.9 (5.8)	27.9 (5.8)
Overweight or Obese	Yes	332 (65%)	320 (64%)
% weight change from baseline: mean(SD)		2.0 (9.2)	1.8 (9.6)
Infection before 30 days	Yes	48 (9%)	73 (13%)
Did patient get adjuvant endocrine therapy	Yes	372 (68%)	367 (67%)
Did patient get adjuvant chemotherapy	Yes	169 (31%)	164 (30%)
15+ nodes removed in AC and SNB	Yes	91 (17%)	276 (51%)
SNB negative	Yes	356 (66%)	363 (68%)

Note: N (%) shown unless indicated otherwise.

Univariate analysis at 5 year visit

Of the 19 potential risk factors in Table 6 only 9 factors were found to be independently associated with CiV_{ips} (Table 7).

Table 7: SNAC univariate analysis at 5 years - factors predicting CiV in the ipsilateral arm

Factor	Estimate	SE	95% CI	P-value
Treatment (SNBM V RAC)	-0.042	0.021	(-0.08 to -0.00)	0.050
CiV contralateral limb	0.906	0.024	(0.86 to 0.95)	<.001
WHO Performance Status (1 v 0)	-0.065	0.049	(-0.16 to 0.03)	0.185
Tumour Palpable (Yes v No)	0.013	0.022	(-0.03 to 0.06)	0.536
Other major concurrent illness (Yes v No)	0.075	0.022	(0.03 to 0.12)	<.001
Diabetes (Yes v No)	0.042	0.048	(-0.05 to 0.14)	0.383
Hypertension (Yes v No)	-0.014	0.026	(-0.07 to 0.04)	0.590
Other illness* (Yes v No)	0.075	0.024	(0.03 to 0.12)	0.002
Age	-0.007	0.001	(-0.01 to -0.00)	<.001
Age 50+ (Yes v No)	-0.127	0.026	(-0.18 to -0.08)	<.001
Weight	0.000	0.001	(-0.00 to 0.00)	0.493
Height	-0.001	0.002	(-0.00 to 0.00)	0.436
BMI	0.001	0.002	(-0.00 to 0.00)	0.617
Overweight or Obese (Yes v No)	-0.002	0.023	(-0.05 to 0.04)	0.921
% weight change from baseline	0.020	0.001	(0.02 to 0.02)	<.001

Factor	Estimate	SE	95% CI	P-value
Infection before 30 days	0.017	0.036	(-0.05 to 0.09)	0.643
Did patient get adjuvant endocrine therapy(Yes v No)	-0.008	0.023	(-0.05 to 0.04)	0.716
Did patient get adjuvant chemotherapy (Yes v No)	0.062	0.023	(0.02 to 0.11)	0.008
15+ nodes removed in AC + SNB (Yes v No)	0.048	0.023	(0.00 to 0.09)	0.032
SNB negative (Yes v No)	-0.064	0.023	(-0.11 to -0.02)	0.006

Note: * Other illness excludes diabetes and hypertension

As noted previously prognostic factors found to be associated independently with CiV_{ips} at a conservative p-value of 0.2 or smaller were considered for inclusion in the full risk set for model selection purposes. Factors included in the full risk set include: 'WHO performance status', 'Other major concurrent illness', 'Other illness (not diabetes or hypertension)', 'Age 50+', '% weight gain from baseline', 'Did patient get adjuvant chemotherapy', '15+ nodes removed in AC and SNB', 'SNB status', 'allocated treatment' and 'CiV_{con}'.

Model selection, the parsimonious model

Model selection was based on the backwards elimination process.

Of the 6 prespecified models, model 5 (the CiV in the ipsilateral arm at 5 years adjusted for treatment and CiV in the contralateral arm) was identified in the simulation experiment as offering the best fit and the most efficient estimator of the treatment effect. As such 'allocated treatment' and 'CiV_{con}' were not included in the risk set as they were to be included in the final model irrespective of whether or not they added anything to the model. A sensitivity analysis was conducted which included 'allocated treatment' and 'CiV_{con}' in the risk set. In both instance the variables retained in the final model were 'allocated treatment' and 'CiV_{con}', 'SNB status', 'Other major concurrent illness' and '% weight gain from baseline' (Table 8).

Table 8: Factors which remain significant in a multivariate analysis (backwards selection).

Parameter	Estimate	95% CI	p-value
Intercept	0.131	(0.085, 0.176)	<.0001

Parameter	Estimate	95% CI	p-value
CiV contralateral limb	0.792	(0.729, 0.856)	<.0001
Treatment (SNBM)	-0.042	(-0.068, -0.017)	0.0010
SNB negative (Yes)	-0.061	(-0.088, -0.034)	<.0001
Other major concurrent illness (Yes)	0.054	(0.028, 0.080)	<.0001
% weight change from baseline	0.004	(0.003, 0.006)	<.0001

Women in the SNBM group had on average a 0.04L (95% CI: 0.07 to 0.02) reduction in CiV_{ips} compared to women in the RAC group. Of the other factors in the parsimonious model 'CiV_{con}' had the largest effect on CiV_{ips} at 5 years. A 1L increase in CiV_{con}' resulted in an increase in CiV_{ips} of 0.79L (95% CI: 0.73 to 0.86). While compared to women who do not report an 'Other major concurrent illness' at baseline those that do have an average increase in CiV_{ips} of 0.05L (95% CI: 0.03 to 0.08). A negative SNB at baseline results on average with a 0.06L (95% CI: 0.09 to 0.03) reduction in CiV_{ips} compared to women with a positive SNB. For a unit increase in '% weight change from baseline' CiV_{ips} increases on average by 0.004L (95% CI: 0.0003 to 0.006).

Diagnostic plots (see appendix) indicate the residuals are plausible normally distributed. Four percent of studentized residuals were found to be greater than ±2. Of the fitted values 57/781 cases had a high leverage (leverage > 2*number of parameters/n) indicating some concern for the potential for outliers to influence analysis. Only 1 case of all fitted values had a Cook's distance measures of greater than 20% while only 3 cases had a measure greater than 10% implying only minor concern, if any, about the influence of outliers on the fit of the regression function.

The treatment effect and assessment of the efficiency of various models

Table 9 presents the estimated coefficients, p-value, adjusted R^2, MSE and the AIC for various models. In particular model a. and b. show univariate analysis of allocated treatment and CiV_{con} respectively against the dependent variable. Model e. shows the

parsimonious model while model d. shows the effect of removing CiV_{con} from model e. The dependent variable in each model is CiV_{ips}.

Table 9: Parameter estimates, R^2 and MSE for various models.

Model	Parameter	Estimate	95% CI	p-value	Adj. R^2	MSE	AIC
a.	Intercept	0.172	(0.106, 0.238)	<.0001	0.003	0.095	-1833
	Treatment (SNBM)	-0.042	(-0.084, 0.000)	0.0506			
b.	Intercept	0.054	(0.041, 0.067)	<.0001	0.639	0.035	-2627
	CiV contralateral limb	0.906	(0.860, 0.953)	<.0001			
c.	Intercept	0.119	(0.080, 0.159)	<.0001	0.644	0.034	-2633
	Treatment (SNBM)	-0.044	(-0.069, -0.019)	0.0007			
	CiV contralateral limb	0.906	(0.860 0.952)	<.0001			
d.	Intercept	0.131	(0.071, 0.190)	<.0001	0.405	0.057	-2233
	Treatment (SNBM)	-0.047	(-0.081, -0.014)	0.0056			
	SNB negative (Yes)	-0.059	(-0.095, -0.023)	0.0013			
	Other major concurrent illness (Yes)	0.106	(0.072, 0.140)	<.0001			
	% weight change from baseline	0.020	(0.019, 0.022)	<.0001			
e.	Intercept	0.131	(0.085, 0.176)	<.0001	0.664	0.032	-2678
	Treatment (SNBM)	-0.042	(-0.068, -0.017)	0.0010			
	CiV contralateral limb	0.792	(0.729, 0.856)	<.0001			
	SNB negative (Yes)	-0.061	(-0.088, -0.034)	<.0001			
	Other major concurrent illness (Yes)	0.054	(0.028, 0.080)	<.0001			
	% weight change from baseline	0.004	(0.003, 0.006)	<.0001			

A simple linear regression of the dependent variable allocated treatment against the independent variable CiV_{ips} (model a) reveals that univariately treatment is not associated with CiV_{ips}. On average, compared to the RAC group the SNBM group have a 0.042L reduction in CiV_{ips}, the 95% CI indicates that this reduction could be as high as 0.084L or as little as 0.0L. When CiV_{con} is added to treatment alone (model c), the strength of this association is increased where compared to the RAC group the SNBM group have a 0.044L (95% CI: 0.069 to 0.019, p=0.0007) reduction in CiV_{ips}. In the parsimonious model (model e), allocated treatment is still found to be associated with CiV_{ips}. In this instance the estimate of the treatment effect is the same as that of the

univariate analysis 0.042L (95% CI: 0.068 to 0.017) but the 95% confidence interval for this estimate has been reduced.

Looking at the MSE for models a. to e. (Table 9) we observe that model a. (univariate analysis of treatment against CiV_{ips}) has the highest MSE (0.095) while model e. (the parsimonious model) has the lowest (0.032). Model e. represents ~.3 fold improvement in the MSE over model a, 0.5 fold improvement over model d and, 0.91 and 0.94 fold improvement over models b and c respectively.

Univariate analysis of treatment against CiV_{ips} (model a) has an adj. R^2 of 0.003 indicating that more than 99% of the variability in the model is unaccounted for by treatment alone. When CiV_{con} is added to the treatment alone (model b), the estimated adj. R^2 is 64%, an improvement in the adj. R^2 of over 60% over model a. For the parsimonious model (model e) the adj. R^2 value is 0.66 indicating that 33% of the variability is unaccounted for by the model. Model e only offer only a 1.03 fold improvement over model b in adj. R^2, implying that the majority of the variability in the model is explained by CiV_{con}. The addition of CiV_{con} to model d results in model e; the improvement in adj. R^2 as a result of adding CiV_{con} to model d. is 26% representing a 1.6 fold improvement in adj. R^2.

The additively of the R^2 indicates that the covariates are uncorrelated to each other. For models d and e ($0.635+0.410 \neq 0.666$) we cannot conclude that the covariates are uncorrelated to each other.

An analysis of the collinearity of the dependent variables in model e is presented in Table 10. Draper et al (1998) suggest that a condition number of 30 or more is conventionally considered to indicate moderate to severe collinearity. In this instance the largest condition number observed is $(3.35/0.04739)^{1/2} = 8.4$ indicating low (or no) concern for collinearity. Note though that 'CiV_{con}' and '% Weight change' have large variance proportions (greater than 50%) though their condition index is only 3.4 thus representing only a slight concern for collinearity.

Of all models considered (Table 9) model e has the smallest AIC. In terms of the AIC, MSE and R_2 value model e. offer the best fit to the data.

Table 10: Collinearity diagnostics for model e. treatment and the CiV_{cont} added to the parsimonious model

			Proportion of Variation					
#	Eigenvalue	Condition Index	Intercept	SNB -ve	Other... illness	% Weight change	Treatment	CiV_{cont}
1	3.35	1	0.00628	0.02137	0.02788	0.00552	0.00781	0.00671
2	1.55016	1.46983	9.3*10-4	0.00439	0.00911	0.15080	0.00124	0.14321
3	0.52620	2.52277	0.00501	0.07380	0.77114	0.02837	0.00771	0.04803
4	0.28850	3.40710	$7.8*10^{-4}$	0.11450	0.08422	0.71788	0.00384	0.72979
5	0.23881	3.74483	0.03121	0.69121	0.09303	0.09659	0.11365	0.07225
6	0.04739	8.40644	0.95579	0.09474	0.01462	$8.4*10^{-4}$	0.86575	$1.4*10^{-5}$

Conclusion:

The primary aim of the report was to discern whether the inclusion of the contralateral arm volume added efficiency gains to the regression models designed to detect lymphedema and thus enable improvements in the estimate of the treatment effect. From the simulation experiment and analysis of the SNAC data we observed that inclusion of the contralateral limb data decreases the residual variability in regression models. Further, inclusion of the contralateral limb data reduces MSE thus offering more accurate estimates of regression parameters while controlling for bias. These results then support the hypothesis that inclusion of the contralateral limb data helps account for confounding factors such as weight and muscle change over time and thus potentially offer more accurate and efficient regression estimates.

The univariate analysis of the SNAC data suggests that SNBM offers little or no benefit over RAC at 5 years. However, the efficiency gains in the treatment estimate resulting from the addition of the contralateral limb data to regression models lead to conclusions which supports the hypothesis that sentinel node biopsy (and axillary clearance in node positive patients) results in less morbidity compared to RAC.

Therefore, upon adjusting for potential confounding factors such as weight and muscle change over time, we have demonstrated that SNBM offers a clear advantage over RAC alone.

It is interesting to note how the conclusion of a RCT can be affected by specification of the analysis of the primary outcome. If the pre-specified analysis or primary outcome of the SNAC trial had been a simple linear regression (or t-test) of CiV_{ips} the trial conclusion would have been negative. Alternatively if the pre-specified analysis had included appropriate adjustment of confounding factors the conclusion would be other.

It is clear then, for a well-run RCT the primary outcome and the statistical methods that will be used should be pre-specified. In order to do this a high level of understanding of the mechanisms that will modify outcomes need to be understood. In some instances this may not be possible; it is in these situations that a well-run simulation experiment comes into its own.

APPENDIX:

Derivation of the treatment effect for the simulated data.

The following gives the derivation of the treatment effect for the 6 pre-specified models. To facilitate the derivation population parameters where used as specified in Table 4.

Let:

- V_{ips} be a n*1 vector of the ipsilateral arm volumes at 5 years,
- CiV_{ips} be a n*1 vector of the change in ipsilateral arm volumes at 5 years from baseline,
- CiV_{con} be a n*1 vector of the change in contralateral arm volumes at 5 years from baseline,
- S_n is a n*1 vector of 1's and 0's, 1 indicating a positive sentinel node biopsy results and 0 otherwise,
- β_0 , β_1 and β_2 are the regression coefficients which are to be estimated,
- X_t is a n*1 vector of 1's and 0's designating the allocated treatment arm (1=SNBM)
- X_{Vips} is a n*1 vector of the ipsilateral arm volumes at baseline,
- X_{Con} is a n*1 vector of the contralteral arm volumes at baseline,
- X_{CiVcon} is a n*1 vector of the CiV in the contralteral arm,
- ϵ is a n*1 vector of standard normally errors.

Model 1: The regression model for V_{ips} at 5 years adjusted for treatment can be written as

1.1 $$V_{ips}=\beta_0+\beta_1 X_t+\epsilon$$

Taking expectation of both sides and setting X_t to be equal to '1' or '0' we have

1.2 $$E(V_{ips}|X_t=1)=\beta_0+\beta_1$$

and

1.3 $$E(V_{ips}|X_t=0)=\beta_0$$

From Table 4 the expected 5 year arm volume for the ipsilateral limb in the RAC group is 2.59, thus from equation 1.3 we have β_0 = 2.59.

The mean vector and covariance matrix for the SNBM group was randomly given by that of the RAC group with probability π. By taking the sum of the expectation of

ipsilateral arm volume in the SNBM group over the disjoint union of the events S_n=1 and S_n=0, and recalling that the expected 5 year arm volume for the ipsilateral limb in the SNBM group is 2.59 and 2.56 given a positive sentinel node or negative SNB respectively; the expected 5 year volume for the ipsilateral limb in the SNBM group is then

$$\begin{aligned} & E(V_{ips} | X_t = 1) \\ & = E(V_{ips} | X_t = 1,\ S_n = 1)\ P(S_n = 1) + E(V_{ips} | X_t = 1,\ S_n = 0)\ P(S_n = 0) \\ & = 2.59\pi + 2.56(1-\pi) \end{aligned} \quad 1.4$$

Subtracting equation 1.3 from 1.2 gives

$$E(V_{ips} | X_t = 1) - E(V_{ips} | X_t = 0) = \beta_1 \quad 1.5$$

the left hand side (LHS) of 1.5 is

$$2.59\pi + 2.56(1-\pi) - 2.59 = (2.56 - 2.59)(1-\pi) \quad 1.6$$

thus β_1 = -0.03(1-π).

Model 2: for the model V_{ips} adjusted for treatment and baseline ipsilateral arm volume write

$$V_{ips} = \beta_0 + \beta_1 X_t + \beta_2 X_{Vips} + \epsilon \quad 2.1$$

Taking expectation of both sides and setting X_t to be equal to '1' or '0' we have

$$E(V_{ips} | X_t = 1) = \beta_0 + \beta_1 + \beta_2 E(X_{Vips} | X_t = 1) \quad 2.2$$

and

$$E(V_{ips} | X_t = 0) = \beta_0 + \beta_2 E(X_{Vips} | X_t = 0) \quad 2.3$$

Note that from the Table 4, the expected baseline ipsilateral arm volume is 2.45 respectively in both treatment groups then subtracting equation 2.3 from 2.2 gives

$$E(V_{ips} | X_t = 1) - E(V_{ips} | X_t = 0) = \beta_1 \quad 2.4$$

using result 1.5 and 1.6 we have the treatment effect β_1 = -0.03(1-π).

Model 3: CiV_{ips} adjusted for treatment write

$$CiV_{ips} = \beta_0 + \beta_1 X_t + \epsilon \quad 3.1$$

Taking expectation of both sides and setting X_t to be equal to '1' or '0' we have

3.2 $$E(CiV_{ips}|X_t=1)=\beta_0+\beta_1$$

and

3.3 $$E(CiV_{ips}|X_t=0)=\beta_0$$

Subtracting equation 3.3 from 3.2 gives

3.4 $$E(CiV_{ips}|X_t=1)-E(CiV_{ips}|X_t=0)=\beta_1$$

Looking at the 2 parts of the LHS of equation 3.4 separately and note that the CiV_{ips} is given by the difference in volumes between baseline and 5 years the expected CiV_{ips} in the RAC group is given by

$$\begin{aligned} & E(CiV_{ips}|X_t=0) \\ & =E(V_{ips}-X_{ips}|X_t=0) \\ & =E(V_{ips}|X_t=0)-E(X_{ips}|X_t=0) \\ 3.5 \quad & =2.59-2.45 \end{aligned}$$

The expected CiV_{ips} in the SNBM group

3.6 $$E(CiV_{ips}|X_t=1)=E(V_{ips}|X_t=1)-E(X_{ips}|X_t=1)$$

The first part of the right hand side (RHS) of the equation is given by the results 1.4, that is 2.59π +2.56(1-π). The second part of then RHS of 3.6 gives

$$\begin{aligned} & E(X_{ips}|X_t=1) \\ & =E(X_{ips}|X_t=1,\ S_n=1)'P(S_n=1)+E(X_{ips}|X_t=1,\ S_n=0)'P(S_n=0) \\ 3.7 \quad & =2.45\pi+2.45(1-\pi) \end{aligned}$$

Substituting 1.4 and 3.7 into 3.6 we have

$$\begin{aligned} E(CiV_{ips}|X_t=1) \quad & =2.59\pi+2.56(1-\pi)-(2.45\pi+2.45(1-\pi)) \\ 3.8 \quad & =2.59\pi+2.56(1-\pi)-2.45 \end{aligned}$$.

Using results 3.8 and 3.5 it follows that the estimated treatment effect β_1 is

$$
\begin{aligned}
&\beta_1 \\
&= E(CiV_{ips} | X_t = 1) - E(CiV_{ips} | X_t = 0) \\
&= 2.59\pi + 2.56(1-\pi) - 2.45 - (2.59 - 2.45) \\
&= 2.59\pi + 2.56(1-\pi) - 2.59 \\
&= -0.03(1-\pi)
\end{aligned}
$$

3.9

thus the treatment effect $\beta_1 = -0.03(1-\pi)$.

Model 4: for CiV_{ips} adjusted for treatment and baseline V_{ips} write

$$CiV_{ips} = \beta_0 + \beta_1 X_t + \beta_2 X_{Vips} + \epsilon$$

Taking expectation of both sides and setting X_t to be equal to '1' or '0' we have

$$E(CiV_{ips} | X_t = 1) = \beta_0 + \beta_1 + \beta_2 E(X_{Vips} | X_t = 1)$$

and

$$E(CiV_{ips} | X_t = 0) = \beta_0 + \beta_2 E(X_{Vips} | X_t = 1) \ .$$

Taking the difference of both and noting that

$$E(X_{Vips} | X_t = 1) = E(X_{Vips} | X_t = 0)$$

we have

$$E(CiV_{ips} | X_t = 1) - E(CiV_{ips} | X_t = 0) = \beta_1$$

which from the results of equation 3.9 we know the treatment effect $\beta_1 = -0.03(1-\pi)$.

Model 5: for CiV_{ips} adjusted for treatment and CiV_{con} write

$$CiV_{ips} = \beta_0 + \beta_1 X_t + \beta_2 X_{CiVcon} + \epsilon$$

Taking expectation of both sides and setting X_t to be equal to '1' or '0' we have

$$E(CiV_{ips} | X_t = 1) = \beta_0 + \beta_1 + \beta_2 E(X_{CiVcon} | X_t = 1)$$

and

$$E(CiV_{ips} | X_t = 0) = \beta_0 + \beta_2 E(X_{CiVcon} | X_t = 1) \ .$$

Taking the difference of both we have

$$E(CiV_{ips} | X_t = 1) - E(CiV_{ips} | X_t = 0) = \beta_1 - \beta_2 \left(E(X_{CiVcon} | X_t = 1) - E(X_{CiVcon} | X_t = 0) \right)$$

Note that the multiplicand of β_2 is equal to zero as the baseline and 5 year contralateral arm volumes for the RAC group and SNBM group are respectively 2.45 and 2.53.

Then from the results of equation 3.9 we have the treatment effect $\beta_1 = -0.03(1-\pi)$.

Model 6: δCiV adjusted for treatment.

$$\delta CiV_{ips} = \beta_0 + \beta_1 X_t + \epsilon$$

Taking expectation of both sides and setting X_t to be equal to '1' or '0' we have

$$E(\delta CiV_{ips} | X_t = 1) = \beta_0 + \beta_1$$

and

$$E(\delta CiV_{ips} | X_t = 0) = \beta_0$$

Taking the difference of both we have

$$E(\delta CiV_{ips} | X_t = 1) - E(\delta CiV_{ips} | X_t = 0) = \beta_1$$

Looking at the expected δCiV in the RAC group we have

$$\begin{aligned} & E(\delta CiV_{ips} | X_t = 0) \\ &= E(CiV_{ips} - CiV_{con} | X_t = 0) \\ &= E(CiV_{ips} | X_t = 0) - E(CiV_{con} | X_t = 0) \end{aligned}$$

Similarly in the SNBM group

$$E(\delta CiV_{ips} | X_t = 0) = E(CiV_{ips} | X_t = 1) - E(CiV_{con} | X_t = 1)$$

β_1 the difference of the expectations is then

$$E(CiV_{ips} | X_t = 1) - E(CiV_{con} | X_t = 1) - (E(CiV_{ips} | X_t = 0) - E(CiV_{con} | X_t = 0))$$

Note that the differences of the expectation for the contralateral arm between the treatment groups

$$E(CiV_{con} | X_t = 1) - E(CiV_{con} | X_t = 0) = 0$$

since the baseline and 5 year contralateral arm volumes for the RAC group and SNBM group are respectively 2.45 and 2.53. β_1 the difference of the expectations reduces to

$$\beta_1 = E(CiV_{ips} | X_t = 1) - E(CiV_{ips} | X_t = 0)$$

which from the results of equation 3.9 we have the treatment effect $\beta_1 = -0.03(1-\pi)$.

The various simulations undertaken vary the 5 year arm volume in the ipsilateral limb while that of the contralateral stays fixed. Denote the mean of 5 year arm volume in the ipsilateral given a negative SNB as μ_{ips} and the 5 year arm volume in the contralateral limb as μ_{con}, and their difference as μ. Then the RHS of 1.6 is then $(\mu_{ips}-\mu_{con})(1-\pi)=\mu(1-\pi)$.

In the general case we have the estimated treatment effect $\beta_1 = \mu(1-\pi)$.

Simulation experiment results

Table 11:Model fit statistics for various scenarios

	Model	β_{treat}	Var(β_{treat})	CI treat	bias	MSE	R^2	Adj R^2	AIC
Covariance moderate									
π=0.3, 1:1 Treatment allocation									
μ=0.0	1	0.002	0.001582	(-0.074 ,0.078)	0.002	0.395	0.001	0.000	-928
	2	0.000	0.000485	(-0.042 ,0.044)	0.000	0.123	0.689	0.688	-2094
	3	0.000	0.000491	(-0.041 ,0.044)	0.000	0.125	0.001	-0.000	-2079
	4	0.000	0.000485	(-0.042 ,0.044)	0.000	0.123	0.018	0.016	-2094
	5	0.001	0.000160	(-0.024 ,0.025)	0.001	0.040	0.679	0.678	-3213
	6	0.001	0.000181	(-0.025 ,0.027)	0.001	0.045	0.001	0.000	-3101
μ=-0.03	1	-0.029	0.001605	(-0.107 ,0.051)	-0.000	0.395	0.002	0.001	-929
	2	-0.030	0.000486	(-0.073 ,0.013)	-0.001	0.123	0.689	0.688	-2094
	3	-0.030	0.000491	(-0.072 ,0.013)	-0.001	0.125	0.003	0.002	-2079
	4	-0.030	0.000486	(-0.073 ,0.013)	-0.001	0.123	0.020	0.018	-2094
	5	-0.030	0.000160	(-0.056 ,-0.005)	-0.001	0.040	0.679	0.678	-3212
	6	-0.030	0.000188	(-0.057 ,-0.005)	-0.001	0.045	0.006	0.005	-3100
μ=-0.06	1	-0.060	0.001670	(-0.135 ,0.020)	-0.001	0.396	0.003	0.002	-926
	2	-0.061	0.000545	(-0.108 ,-0.016)	-0.002	0.123	0.690	0.689	-2092
	3	-0.061	0.000549	(-0.109 ,-0.017)	-0.002	0.125	0.008	0.007	-2078
	4	-0.061	0.000545	(-0.108 ,-0.016)	-0.002	0.123	0.024	0.023	-2092
	5	-0.061	0.000171	(-0.085 ,-0.035)	-0.002	0.040	0.681	0.681	-3212
	6	-0.061	0.000185	(-0.086 ,-0.033)	-0.002	0.045	0.021	0.020	-3101
1:1 Treatment allocation, μ=-0.03									
π=0.1	1	-0.032	0.001620	(-0.107 ,0.052)	-0.002	0.395	0.002	0.001	-927
	2	-0.030	0.000484	(-0.074 ,0.013)	-0.001	0.123	0.688	0.688	-2091
	3	-0.030	0.000486	(-0.072 ,0.012)	-0.001	0.125	0.003	0.002	-2076

	Model	β_{treat}	Var(β_{treat})	CI treat	bias	MSE	R^2	Adj R^2	AIC
	4	-0.030	0.000484	(-0.074 ,0.013)	-0.001	0.123	0.019	0.017	-2091
	5	-0.030	0.000159	(-0.053 ,-0.004)	0.000	0.040	0.679	0.679	-3210
	6	-0.029	0.000174	(-0.054 ,-0.003)	0.000	0.045	0.006	0.005	-3098
π=0.3	1	-0.028	0.001545	(-0.101 ,0.050)	0.001	0.394	0.001	0.000	-930
	2	-0.030	0.000502	(-0.072 ,0.014)	-0.000	0.123	0.689	0.688	-2095
	3	-0.030	0.000512	(-0.073 ,0.014)	-0.001	0.125	0.003	0.002	-2080
	4	-0.030	0.000502	(-0.072 ,0.014)	-0.000	0.123	0.020	0.018	-2095
	5	-0.030	0.000151	(-0.054 ,-0.006)	-0.001	0.040	0.679	0.679	-3214
	6	-0.030	0.000167	(-0.056 ,-0.005)	-0.001	0.045	0.006	0.005	-3103
π=0.5	1	-0.031	0.001686	(-0.111 ,0.047)	-0.002	0.395	0.002	0.001	-927
	2	-0.031	0.000471	(-0.076 ,0.011)	-0.002	0.123	0.689	0.688	-2092
	3	-0.031	0.000471	(-0.077 ,0.009)	-0.002	0.125	0.003	0.002	-2078
	4	-0.031	0.000471	(-0.076 ,0.011)	-0.002	0.123	0.019	0.017	-2092
	5	-0.030	0.000156	(-0.056 ,-0.006)	-0.002	0.040	0.679	0.679	-3211
	6	-0.030	0.000176	(-0.057 ,-0.004)	-0.002	0.045	0.006	0.005	-3099
π=0.3, μ=-0.03									
Rnd=1:2	1	-0.033	0.001828	(-0.118 ,0.050)	-0.004	0.390	0.002	0.001	-941
	2	-0.031	0.000618	(-0.081 ,0.017)	-0.002	0.115	0.705	0.705	-2160
	3	-0.031	0.000617	(-0.081 ,0.017)	-0.002	0.117	0.003	0.002	-2146
	4	-0.031	0.000618	(-0.081 ,0.017)	-0.002	0.115	0.019	0.017	-2160
	5	-0.031	0.000216	(-0.060 ,-0.001)	-0.002	0.034	0.706	0.705	-3366
	6	-0.031	0.000231	(-0.060 ,0.001)	-0.001	0.040	0.006	0.005	-3219

Covariance week

	Model	β_{treat}	Var(β_{treat})	CI treat	bias	MSE	R^2	Adj R^2	AIC
π=0.3, 1:1 Treatment allocation									
μ=0.00	1	-0.000	0.000641	(-0.051 ,0.046)	-0.000	0.158	0.001	0.000	-1842
	2	-0.000	0.000216	(-0.030 ,0.028)	-0.000	0.049	0.689	0.688	-3007
	3	-0.000	0.000218	(-0.031 ,0.028)	-0.000	0.050	0.001	0.000	-2993
	4	-0.000	0.000216	(-0.030 ,0.028)	-0.000	0.049	0.018	0.016	-3007
	5	-0.000	0.000068	(-0.017 ,0.015)	-0.000	0.016	0.679	0.678	-4127
	6	0.000	0.000075	(-0.017 ,0.017)	0.000	0.018	0.001	0.000	-4016
μ=-0.03	1	-0.030	0.000582	(-0.078 ,0.019)	-0.001	0.158	0.002	0.001	-1845
	2	-0.029	0.000203	(-0.056 ,-0.001)	-0.000	0.049	0.689	0.688	-3008
	3	-0.029	0.000208	(-0.057 ,-0.001)	-0.000	0.050	0.005	0.004	-2993
	4	-0.029	0.000203	(-0.056 ,-0.001)	-0.000	0.049	0.022	0.020	-3008
	5	-0.030	0.000063	(-0.045 ,-0.014)	-0.001	0.016	0.681	0.680	-4130

	Model	β_{treat}	Var(β_{treat})	CI treat	bias	MSE	R^2	Adj R^2	AIC
	6	-0.030	0.000070	(-0.046 ,-0.014)	-0.001	0.018	0.013	0.012	-4019
μ=-0.06	1	-0.059	0.000660	(-0.107 ,-0.011)	-0.001	0.158	0.007	0.006	-1845
	2	-0.059	0.000204	(-0.087 ,-0.032)	-0.001	0.049	0.690	0.690	-3009
	3	-0.059	0.000205	(-0.086 ,-0.032)	-0.001	0.050	0.018	0.017	-2994
	4	-0.059	0.000204	(-0.087 ,-0.032)	-0.001	0.049	0.035	0.033	-3009
	5	-0.060	0.000062	(-0.075 ,-0.045)	-0.002	0.016	0.685	0.684	-4130
	6	-0.060	0.000068	(-0.076 ,-0.045)	-0.002	0.018	0.049	0.048	-4019
π=0.3, 1:1 Treatment allocation, μ=-0.03									
π=0.1	1	-0.030	0.000625	(-0.079 ,0.021)	-0.001	0.158	0.002	0.001	-1843
	2	-0.030	0.000192	(-0.058 ,-0.004)	-0.001	0.049	0.690	0.689	-3010
	3	-0.030	0.000195	(-0.058 ,-0.003)	-0.001	0.050	0.006	0.005	-2995
	4	-0.030	0.000192	(-0.058 ,-0.004)	-0.001	0.049	0.022	0.020	-3010
	5	-0.030	0.000064	(-0.046 ,-0.014)	-0.001	0.016	0.681	0.680	-4130
	6	-0.030	0.000072	(-0.047 ,-0.013)	-0.001	0.018	0.014	0.013	-4018
π=0.3	1	-0.030	0.000649	(-0.077 ,0.022)	-0.001	0.158	0.002	0.001	-1844
	2	-0.030	0.000204	(-0.057 ,-0.003)	-0.001	0.049	0.689	0.689	-3010
	3	-0.030	0.000205	(-0.057 ,-0.003)	-0.001	0.050	0.006	0.005	-2995
	4	-0.030	0.000204	(-0.057 ,-0.003)	-0.001	0.049	0.022	0.020	-3010
	5	-0.030	0.000067	(-0.047 ,-0.015)	-0.001	0.016	0.679	0.678	-4125
π=0.3	6	-0.030	0.000074	(-0.047 ,-0.014)	-0.001	0.018	0.014	0.013	-4013
π=0.5	1	-0.029	0.000652	(-0.078 ,0.024)	-0.001	0.158	0.002	0.001	-1844
	2	-0.030	0.000195	(-0.057 ,-0.003)	-0.002	0.049	0.689	0.688	-3009
	3	-0.030	0.000199	(-0.057 ,-0.003)	-0.002	0.050	0.006	0.005	-2994
	4	-0.030	0.000195	(-0.057 ,-0.003)	-0.002	0.049	0.022	0.020	-3009
	5	-0.030	0.000063	(-0.045 ,-0.015)	-0.001	0.016	0.680	0.680	-4128
	6	-0.030	0.000072	(-0.046 ,-0.014)	-0.001	0.018	0.013	0.012	-4016
π=0.3, μ=-0.03									
Rnd=1:2	1	-0.030	0.000750	(-0.083 ,0.025)	-0.001	0.155	0.002	0.001	-1860
	2	-0.030	0.000243	(-0.061 ,0.000)	-0.001	0.046	0.705	0.705	-3079
	3	-0.030	0.000246	(-0.061 ,0.001)	-0.000	0.047	0.005	0.004	-3065
	4	-0.030	0.000243	(-0.061 ,0.000)	-0.001	0.046	0.021	0.019	-3079
	5	-0.030	0.000083	(-0.048 ,-0.013)	-0.001	0.014	0.706	0.705	-4283
	6	-0.030	0.000087	(-0.049 ,-0.013)	-0.001	0.016	0.014	0.013	-4136

Covariance high

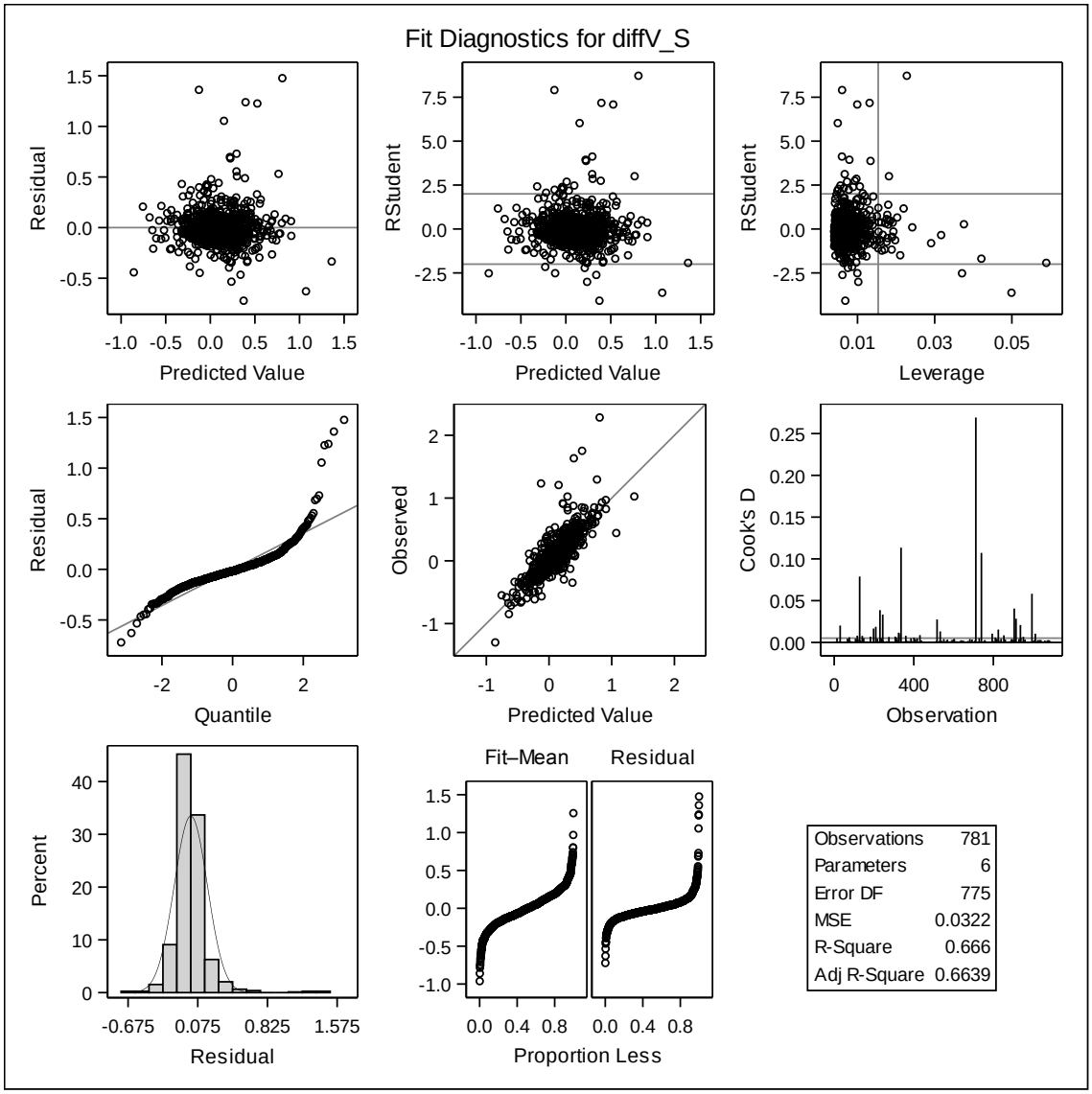
	Model	β_{treat}	Var(β_{treat})	CI treat	bias	MSE	R2	Adj R2	AIC

	Model	β_{treat}	Var(β_{treat})	CI treat	bias	MSE	R2	Adj R2	AIC
π=0.3, 1:1 Treatment allocation									
μ=0.00	1	0.003	0.003332	(-0.112 ,0.117)	0.003	0.888	0.001	-0.000	-117
	2	-0.000	0.001024	(-0.066 ,0.064)	-0.000	0.277	0.689	0.688	-1283
	3	-0.001	0.001048	(-0.065 ,0.066)	-0.001	0.281	0.001	-0.000	-1268
	4	-0.000	0.001024	(-0.066 ,0.064)	-0.000	0.277	0.018	0.016	-1283
	5	0.000	0.000344	(-0.036 ,0.036)	0.000	0.091	0.678	0.678	-2400
	6	0.001	0.000394	(-0.039 ,0.039)	0.001	0.101	0.001	-0.000	-2288
μ=-0.03	1	-0.028	0.003644	(-0.146 ,0.089)	0.002	0.888	0.001	0.000	-118
	2	-0.030	0.001097	(-0.094 ,0.035)	-0.001	0.277	0.689	0.688	-1283
	3	-0.030	0.001123	(-0.095 ,0.034)	-0.001	0.281	0.002	0.001	-1268
	4	-0.030	0.001097	(-0.094 ,0.035)	-0.001	0.277	0.019	0.017	-1283
	5	-0.029	0.000383	(-0.067 ,0.009)	-0.000	0.091	0.678	0.678	-2399
	6	-0.029	0.000426	(-0.067 ,0.012)	-0.000	0.102	0.003	0.002	-2287
μ=-0.06	1	-0.057	0.003230	(-0.160 ,0.054)	0.001	0.887	0.002	0.001	-119
	2	-0.059	0.001069	(-0.124 ,0.007)	-0.001	0.276	0.689	0.688	-1284
	3	-0.059	0.001104	(-0.125 ,0.008)	-0.001	0.281	0.004	0.003	-1269
	4	-0.059	0.001069	(-0.124 ,0.007)	-0.001	0.276	0.021	0.019	-1284
	5	-0.060	0.000345	(-0.095 ,-0.022)	-0.001	0.090	0.680	0.680	-2405
	6	-0.060	0.000398	(-0.099 ,-0.021)	-0.001	0.101	0.010	0.009	-2292
1:1 Treatment allocation, μ=-0.03									
π=0.1	1	-0.029	0.003502	(-0.148 ,0.092)	0.001	0.888	0.001	0.000	-118
	2	-0.031	0.001121	(-0.094 ,0.038)	-0.001	0.276	0.689	0.689	-1285
	3	-0.031	0.001151	(-0.093 ,0.038)	-0.001	0.280	0.002	0.001	-1270
	4	-0.031	0.001121	(-0.094 ,0.038)	-0.001	0.276	0.018	0.016	-1285
	5	-0.031	0.000336	(-0.067 ,0.005)	-0.001	0.090	0.678	0.678	-2402
	6	-0.031	0.000379	(-0.070 ,0.007)	-0.001	0.101	0.003	0.002	-2289
π=0.3	1	-0.031	0.003722	(-0.150 ,0.093)	-0.002	0.889	0.001	0.000	-117
	2	-0.031	0.001117	(-0.096 ,0.034)	-0.002	0.278	0.688	0.687	-1279
	3	-0.031	0.001115	(-0.097 ,0.035)	-0.002	0.282	0.002	0.001	-1264
	4	-0.031	0.001117	(-0.096 ,0.034)	-0.002	0.278	0.019	0.017	-1279
	5	-0.031	0.000368	(-0.069 ,0.007)	-0.001	0.090	0.680	0.679	-2401
	6	-0.031	0.000410	(-0.072 ,0.009)	-0.001	0.101	0.003	0.002	-2290
π=0.5	1	-0.029	0.003748	(-0.149 ,0.088)	-0.001	0.889	0.001	0.000	-117
	2	-0.031	0.001089	(-0.096 ,0.032)	-0.002	0.277	0.689	0.688	-1282
	3	-0.031	0.001101	(-0.095 ,0.035)	-0.002	0.281	0.002	0.001	-1267
	4	-0.031	0.001089	(-0.096 ,0.032)	-0.002	0.277	0.019	0.017	-1282

	Model	β_{treat}	Var(β_{treat})	CI treat	bias	MSE	R2	Adj R2	AIC
	5	-0.030	0.000367	(-0.069 ,0.006)	-0.002	0.090	0.679	0.679	-2402
	6	-0.030	0.000434	(-0.071 ,0.009)	-0.001	0.101	0.003	0.002	-2291
π=0.3, μ=-0.03									
Rnd=1:2	1	-0.027	0.003958	(-0.145 ,0.097)	0.002	0.877	0.001	0.000	-130
	2	-0.029	0.001271	(-0.101 ,0.041)	0.000	0.257	0.707	0.706	-1356
	3	-0.029	0.001283	(-0.099 ,0.041)	-0.000	0.261	0.002	0.001	-1342
	4	-0.029	0.001271	(-0.101 ,0.041)	0.000	0.257	0.017	0.015	-1356
	5	-0.030	0.000455	(-0.071 ,0.012)	-0.001	0.077	0.705	0.704	-2560
	6	-0.030	0.000492	(-0.073 ,0.014)	-0.001	0.090	0.003	0.002	-2412

Model:
1. Ipsilateral arm volume at 5 yrs adjusted for treatment,
2. Model 1 + baseline contralateral arm volume,
3. CiV Ipsilateral arm at 5 yrs adjusted for treatment,
4. Model 3 + baseline contralateral arm volume,
5. Model 3 + CiV contralateral arm,
6. δCiV adjusted for treatment.

Diagnostic plots: Final model



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