Appendix G Clinical guideline technical assessment unit analysis (phosphate binders)

This analysis was carried out by the Clinical Guidelines Technical Support Unit on behalf of the National Institute for Health and Clinical Excellence.

Article I. Management of Hyperphosphataemia: Long term analysis for Calcium (2)

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Summary of work required: Assistance with a network meta-analysis for continuous data at multiple follow-up times

Article II. Summary

Trials report mean Calcium (Ca) levels at various time points from baseline (time 0) to 735 days. Although it is generally accepted that all treatments are equally effective at controlling Ca levels in the short-term, it is thought that some treatments may cause an increase in Ca levels in the long term i.e. after more than 6 months of use. A simple analysis of the mean difference in Ca levels post-6 months (defined as > 180 days) was carried out, where the data inputs are the averages of the means reported at all time points post 180 days and their variances. However, the averaging needs to account for the correlation in the observations at different time points. As this correlation is unknown, it was imputed based on available data. If other sources of information on the within-study correlation at different time points become available, the calculations can easily be redone.

We describe the method used to impute the within-trial correlations at time points with different lags, and for calculating the average and variance of correlated outcomes. The resulting averages and variances are used as data inputs into a standard network meta-analysis (NMA) model in WinBUGS.

Results from fixed effects (FE) and random effects (RE) models are described and the FE model is recommended.

A generalised least squares regression analysis was also conducted for each arm of studies reporting at more than one time point > 180 days, with the aim of determining whether an increasing trend could be detected in the means. No trend was found (all regression slopes were estimated as approximately zero for all treatment arms).

Article III. Data

Data on mean Ca levels are available from 30 trials, comparing 13 treatments. However, restricting the analysis to time points over 180 days, resulted in using data from only 16 trials, comparing 9 treatments. No trials compared 'Placebo', 'Calcium Carbonate (Bread)', 'Sevelamer hydrochloride+Calcium Carbonate' or 'Sevelamer Carbonate' beyond 180 days.

Study 4084 was removed, so 15 trials were used in the final analysis.

Treatments were coded 1 to 9 (Table 1), the data available are described in

Table 2 and the network diagram is presented in Figure 1. Sevelamer hydrochloride was chosen as the overall baseline, or reference treatment, as it was used by most trials and was at the centre of the network (i.e. was involved in several comparisons).

Study 4500 did not report a SD or the number of patients contributing to the mean, therefore the standard error (SE) of the mean was imputed based on information provided by the other studies comparing treatments 1 and 5 (see below).

Article IV. Methods

Section 4.01 Imputing Standard Errors for Study 4500

The SEs of the mean Ca levels for treatments 1 and 5 in Study 4500 were imputed from a linear regression of the SEs of other trials with treatments 1

and 5, respectively. It was decided to include only time points beyond 180 days, as the SEs may vary with time.

Figure 2 shows the available SEs and regression line for treatment 1. The imputed values for the SE of treatment 1 at 196 and 224 days were 0.0471 and 0.0459, respectively.

Figure 3 shows the available data and regression line for treatment 5. The imputed values for the SE of treatment 5 at 196 and 224 days were 0.100 and 0.092, respectively.

If we had chosen to use all the data (i.e. from time 0) the imputed SE for treatment 1 at 196 and 224 days would be 0.0364 and 0.0362, respectively. The imputed SE for treatment 5 at 196 and 224 days would be 0.0643 and 0.0662, respectively. Another option would be to impute the maximum SE observed for treatment 1 at all time points: 0.1, and similarly for treatment 5, the imputed SE would be 0.1.

Section 4.02 Imputing within-study correlations at different time lags

We do not have any prior knowledge on the within-trial correlation of measurements taken at different time points. However, 7 studies report both the mean Ca level in each arm with SD and the mean change from baseline in Ca levels with SD at various time points. Using this information, we can obtain the within trial correlation for each trial at the various time points (Higgins and Green, 2008, Section 16.1). These correlations are given in Table 3 and plotted in Figure 4.

We will assume that there is no difference in correlations between treatments and that the correlations only depend on the time lag between observations, and not on whether they are comparing to baseline or at other time points. We will further assume that there are only 3 different correlations, for time lags falling in three intervals, as follows:

For time lags between 0 and 25 days, the correlation is 0.92

For time lags between 26 and 60 days, the correlation is 0.76

For time lags over 60 days, the correlation is 0.55

These values were obtained as the average of the correlations at time 21, time 56 and all subsequent times (84-364 days), respectively.

If more information becomes available, these assumptions can easily be changed and new pooled means generated.

Section 4.03 Calculating the mean and variance of all means > 180 days

For each arm of each study in

Table 2, let yj be the mean calcium level at time point j and σj the standard deviation of the observations at time point j. For a given study, reporting at J time points (J≥1), we have a vector of observations Y, such that,

$$\mathbf{Y} = \begin{pmatrix} y_1 \\ y_2 \\ \vdots \\ y_J \end{pmatrix} \sim N_J \quad \mathbf{m}, \mathbf{V}$$

where m is a vector of unknown means and V is the variance-covariance matrix, assumed known. Letting Z represent a linear combination of the elements of Y, such that,

$$Z = \frac{y_1 + y_2 + \ldots + y_J}{J} = \mathbf{BY}$$

where

$$\mathbf{B} = \frac{1}{J} \; 1 \quad 1 \quad \ldots \quad 1$$

we have,

$$Var(Z) = \mathbf{BVB'} \qquad (1)$$

For each arm of each study, V has in its diagonal the variances of the mean at each time point, $SE_j^2 = \sigma_j^2 / N$, and the off-diagonal elements in row i, column j, will hold $\rho SE_j SE_i$, where ρ is chosen according to the time lag between observations i and j.

Repeating this method for all arms of each study, we get $Z = y_{i,k}^*$ the average of the mean Ca levels in arm k of study i, (i=1,...,16, k=1,2) with variances calculated using equation (1).

The transformed data, on which the NMA will be carried out, is given in Table 4.

Section 4.04 Relative effects model

The data in Table 4 was used to conduct a NMA, using the model and corresponding WinBUGS code in Dias et al (2011a, Section 3.4).

Briefly, the transformed means are assumed to be normally distributed, so that the likelihood can be written as

$$y_{ik}^* \sim N\ \theta_{ik}, Var_{ik}$$

The parameter of interest is the mean, θ_{ik}, of this continuous measure which is unconstrained on the real line. The model can be written as

$$\theta_{ik} = \mu_i + \delta_{i,1k} I_{\{k \neq 1\}} \qquad (2)$$

with

$$\delta_{i,1k} \sim N(d_{t_{i1},t_{ik}}, \tau^2)$$

$$I_{\{u\}} = \begin{cases} 1 & \text{if } u \text{ is true} \\ 0 & \text{otherwise} \end{cases}$$

where $d_{t_{i1},t_{ik}}$ represents the mean effect of the treatment in arm k in trial i, tik, compared to the treatment in arm 1 of trial i, ti1, and τ2 represents the between-trial variability in treatment effects (heterogeneity). Under the exchangeability (consistency) assumption we can write

$$d_{t_{i1},t_{ik}} = d_{1,t_{ik}} - d_{1,t_{i1}}$$

For a FE model we replace equation (2) with

$$\theta_{ik} = \mu_i + d_{t_{i1},t_{ik}} I_{\{k \neq 1\}}$$

Non-informative N(0,1002) priors are given to the μ's and d's. In a RE model a Uniform(0,10) prior was used for τ.

Article V. Results

Model fit statistics for the FE and RE models are given in Table 5. Although the RE model has a better fit, this is at the expense of more parameters and the DIC does not favour any of the models.

We will therefore prefer the FE model, due to its simplicity and easier interpretation.

A plot of the effects (mean differences) of all treatments relative to treatment 1 for the FE model is given in Figure 5. Effects from the RE model are in Figure 6. The uncertainty in the treatment effects is larger in the RE model. Differences > 0 favour treatment 1.

Treatment 9 appears to be the best treatment and treatments 3 and 6 the worst, although the differences are small and may not be clinically significant. (For more results see attached WinBUGS files)

Section 5.01 Consistency

There is only one evidence loop in this network (Figure 1) formed by treatments 1,5,6. Consistency was checked by comparing the treatment effects obtained from separate pairwise meta-analysis for each pair of

treatments (FE model) using the Bucher approach as recommended in Dias et al. (2011b). No evidence of inconsistency was found (p-value > 0.6).

References

Dias, S., Welton, N. J., Sutton, A. J., & Ades, A. E. 2011a, NICE DSU Technical Support Document 2: A generalised linear modelling framework for pair-wise and network meta-analysis, NICE Decision Support Unit, available from http://www.nicedsu.org.uk/.

Dias, S., Welton, N. J., Sutton, A. J., & Ades, A. E. 2011b, NICE DSU Technical Support Document 4: Inconsistency in networks of evidence based on randomised controlled trials, NICE Decision Support Unit, available from http://www.nicedsu.org.uk/.

Higgins, J. P. T. & Green, S. 2008, Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]. Chichester, The Cochrane Collaboration, Wiley.

Tables

Table 1 Treatment codes. Treatment 1 is assumed to be the baseline reference treatment to which all others are compared.

Treatment code	Treatment name
1	Sevelamer hydrochloride
2	Lanthanum carbonate
3	Any binder
4	Aluminium Hydroxide
5	Calcium acetate
6	Calcium Carbonate
7	Calcium Based Binders
8	Calcium Acetate + Magnesium Carbonate
9	Magnesium Carbonate

Table 2 data available at > 180 days. ‘NA’ denotes data not available. Treatment codes are given in Table 1.

Observation time (in days)	treatment		arm 1			arm 2			
	arm 1	arm 2	N	mean	SD	N	mean	SD	RefID
364	2	6	49	2.33	0.16	49	2.39	0.21	4392
182	2	3	682	2.37	0.4	677	2.5	0.398	4365
238	2	3	682	2.41	0.533	677	2.5	0.531	4365
301	2	3	682	2.45	0.4	677	2.54	0.398	4365
364	2	3	682	2.45	0.4	677	2.54	0.4	4365
427	2	3	682	2.45	0.666	677	2.54	0.4	4365
483	2	3	682	2.4	0.666	677	2.54	0.4	4365
546	2	3	682	2.45	0.533	677	2.54	0.4	4365
609	2	3	682	2.4	0.666	677	2.54	0.4	4365
665	2	3	682	2.45	0.533	677	2.54	0.531	4365
728	2	3	682	2.48	0.666	677	2.53	0.664	4365
182	2	3	51	2.26	0.21	48	2.4	0.21	4744
238	2	3	51	2.28	0.29	48	2.38	0.139	4744
301	2	3	51	2.35	0.29	48	2.38	0.28	4744
364	2	3	51	2.29	0.143	48	2.38	0.21	4744
427	2	3	51	2.31	0.29	48	2.36	0.28	4744
483	2	3	51	2.25	0.29	48	2.36	0.21	4744
546	2	3	51	2.34	0.29	48	2.38	0.21	4744
609	2	3	51	2.26	0.357	48	2.38	0.14	4744

665	2	3	51	2.34	0.214	48	2.41	0.21	4744
735	2	3	51	2.36	0.21	48	2.38	0.28	4744
364	1	5	54	2.37	0.17	54	2.4	0.15	4213
364	1	5	70	2.25	0.17	59	2.35	0.17	4965
456.563	1	6	31	2.3	0.3	41	2.5	0.2	4062
547.875	1	6	31	2.3	0.1	41	2.4	0.2	4062
639.188	1	6	31	2.2	0.2	41	2.4	0.2	4062
730.5	1	6	31	2.2	0.1	41	2.4	0.2	4062
196	1	6	36	2.32	0.18	46	2.46	0.2	4142
224	1	6	36	2.37	0.12	46	2.46	0.136	4142
252	1	6	36	2.35	0.18	46	2.46	0.2	4142
280	1	6	36	2.34	0.18	46	2.45	0.2	4142
308	1	6	36	2.35	0.12	46	2.48	0.2	4142
336	1	6	36	2.35	0.12	46	2.49	0.2	4142
364	1	6	36	2.35	0.12	46	2.47	0.2	4142
364	1	6	91	2.4	0.15	92	2.45	0.2	4593
364	1	7	99	2.37	0.15	101	2.42	0.17	4209
182	1	7	44	2.3	0.27	47	2.31	0.27	4353
210	1	7	44	2.33	0.2	47	2.38	0.343	4353
238	1	7	44	2.31	0.2	47	2.33	0.27	4353
266	1	7	44	2.25	0.27	47	2.36	0.21	4353
294	1	7	44	2.3	0.332	47	2.41	0.21	4353
322	1	7	44	2.31	0.2	47	2.41	0.21	4353
350	1	7	44	2.37	0.27	47	2.45	0.27	4353
378	1	7	44	2.42	0.33	47	2.3	0.21	4353
175	1	8	122	2.189	0.157	122	2.219	0.156	4283
182.625	4	6	6	2.31	0.049	5	2.43	0.045	4574
182.625	5	6	11	2.51	0.199	9	2.51	0.18	4567
243.5	5	6	11	2.57	0.2	9	2.57	0.18	4567
304.375	5	6	11	2.63	0.3	9	2.63	0.27	4567
365.25	5	6	11	2.45	0.2	9	2.45	0.18	4567
182.625	6	9	21	2.42	0.1	25	2.23	0.14	5221
196	1	5	NA	2.50	NA	NA	2.45	NA	4500
224	1	5	NA	2.48	NA	NA	2.48	NA	4500

Table 3 Calculation of within-trial correlations between baseline and time point x.

RefID	treatment	time (x)	sd (change)	sd (at baseline)	sd (at time x)	correlation
5004	5	21	0.08	0.16	0.14	0.8661
5004	6	21	0.08	0.31	0.28	0.9683
4695	3	56	0.217	0.304	0.304	0.7452
4695	5	56	0.234	0.365	0.345	0.7842
4337	3	84	0.14	0.15	0.14	0.5357
4337	5	84	0.21	0.12	0.25	0.5467
4370	3	168	0.2	0.17	0.15	0.2235
4370	12	168	0.17	0.17	0.17	0.5000
4283	3	175	0.152	0.182	0.157	0.6067
4283	9	175	0.179	0.228	0.156	0.6225
4142	3	364	0.1	0.148	0.12	0.7405
4593	3	364	0.195	0.2	0.15	0.4079
4142	6	364	0.16	0.136	0.2	0.6047
4593	6	364	0.152	0.16	0.2	0.6640

Table 4 Transformed means and variances for calcium levels at times > 180 days for input into WinBUGS

treatments		Number of arms	Data				RefID
arm 1	arm 2		arm 1		arm 2		
t[,1]	t[,2]	na[]	y[,1]	Var[,1]	y[,2]	Var[,2]	
2	6	2	2.330	0.000522	2.390	0.000900	4392
2	3	2	2.431	0.000267	2.531	0.000184	4365
2	3	2	2.304	0.000800	2.381	0.000596	4744
1	5	2	2.370	0.000535	2.400	0.000417	4213
1	5	2	2.250	0.000413	2.350	0.000490	4965
1	6	2	2.250	0.000679	2.425	0.000646	4062
1	6	2	2.347	0.000420	2.467	0.000562	4142
1	6	2	2.400	0.000247	2.450	0.000435	4593
1	7	2	2.370	0.000227	2.420	0.000286	4209
1	7	2	2.324	0.001052	2.369	0.000913	4353
1	8	2	2.189	0.000202	2.219	0.000199	4283
4	6	2	2.310	0.000400	2.430	0.000405	4574
5	6	2	2.540	0.003062	2.540	0.003038	4567
6	9	2	2.420	0.000476	2.230	0.000784	5221

1	5	2	2.490	0.001903	2.465	0.008112	4500

Table 5 Model fit statistics for the Calcium long term analysis

	resdev*	pD	DIC	heterogeneity (τ)			
				mean	sd	median	CrI
RE	30.0	26.9	56.9	0.04	0.03	0.04	(0.00,0.10)
FE	35.3	23.0	58.3				

* compare to 30 data points

Figures

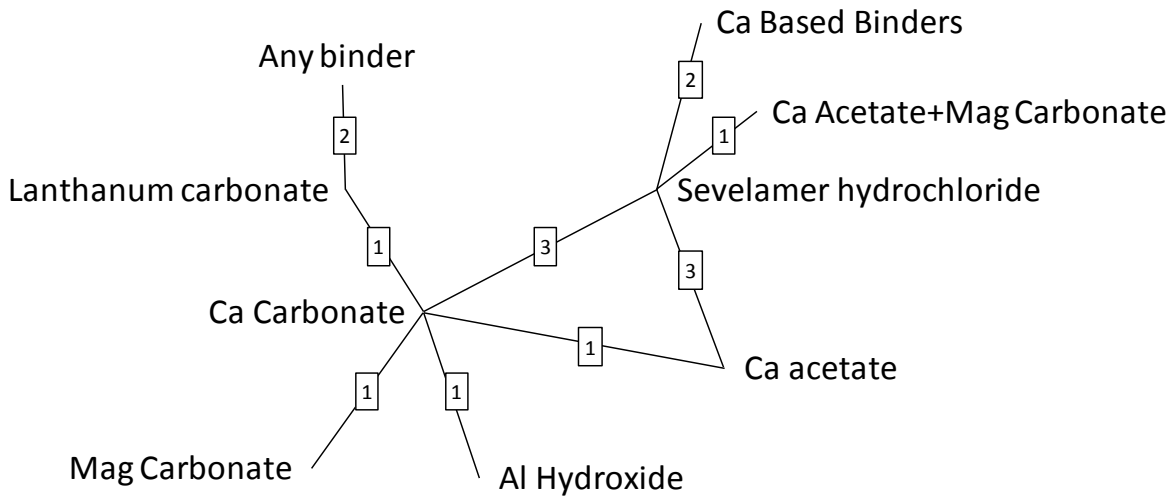

Figure 1 Treatment network mean calcium levels > 18o days: each vertix represents a treatment, connecting lines indicate pairs of treatments which have been directly compared in randomised trials and data >180 days available. The numbers on the lines indicate how many trials were available for each comparison.

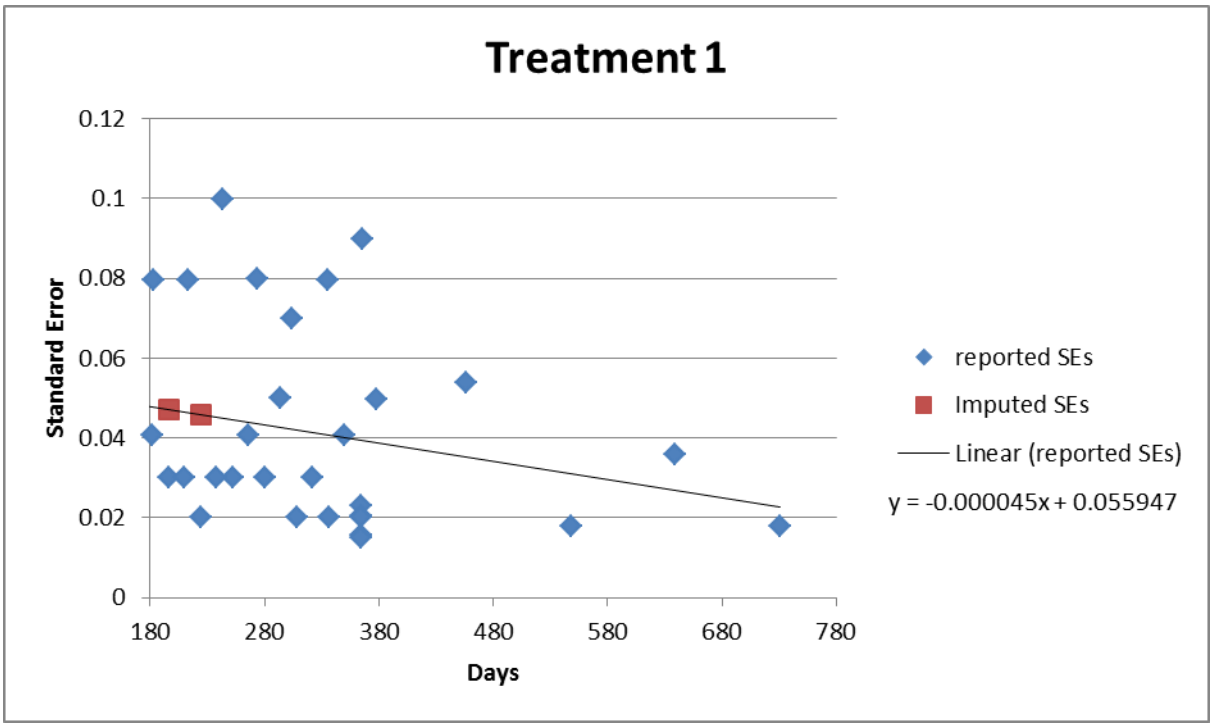

Figure 2 simple linear regression of sE by number of days for all studies comparisng treatment 1 at time points > 180 days.

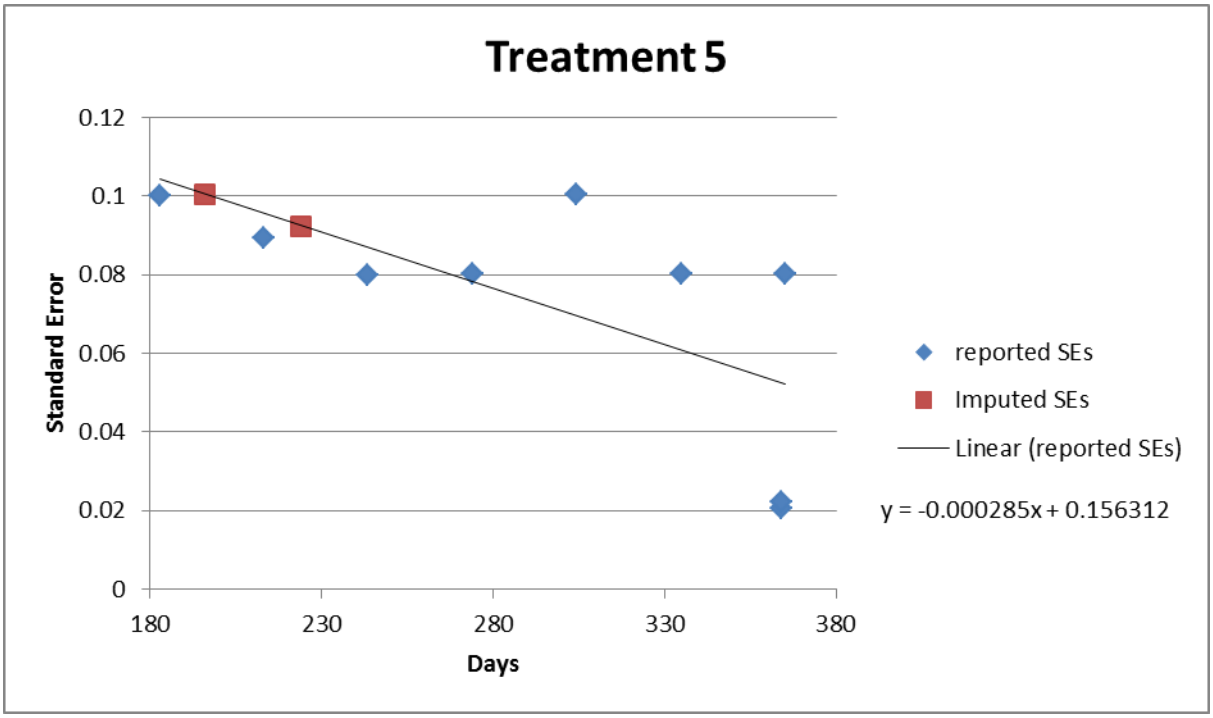

Figure 3 simple linear regression of sE by number of days for all studies comparisng treatment 5 at time points > 180 days.

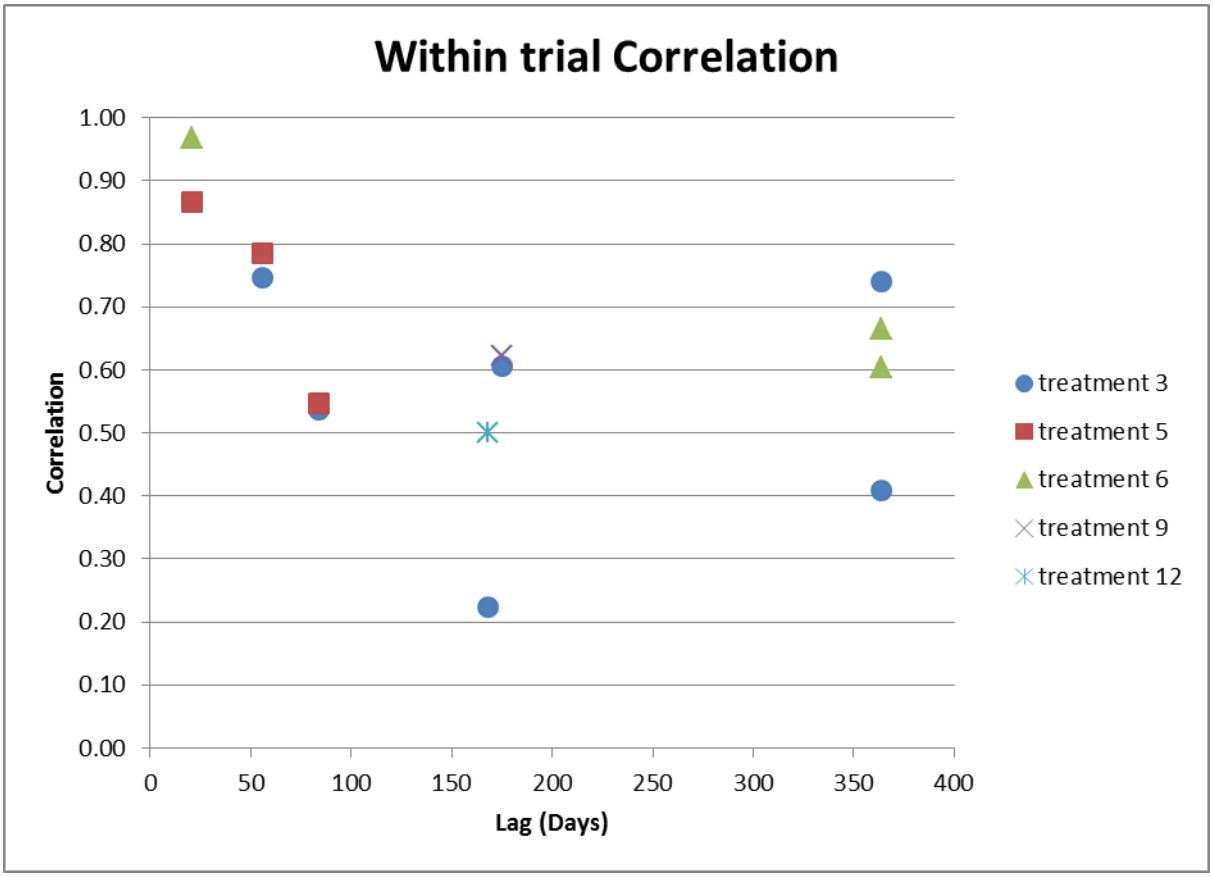

Figure 4 Plot of within-trial correlations. All correlations are relative to baseline observations.

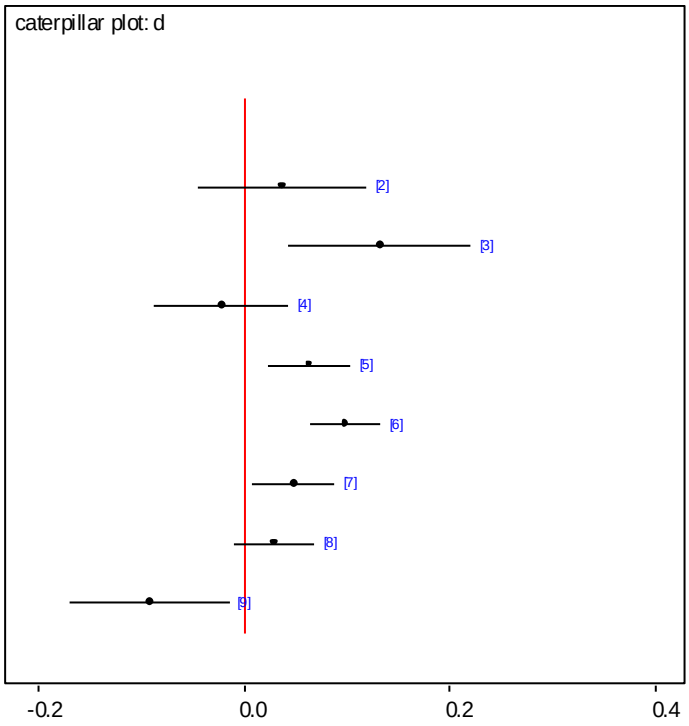

Figure 5 FE model: plot of mean differences of all treatments relative to treatmet 1. Values to the right of the horizontal (red) line favour treatment 1. Treatment codes are given in Table 1.

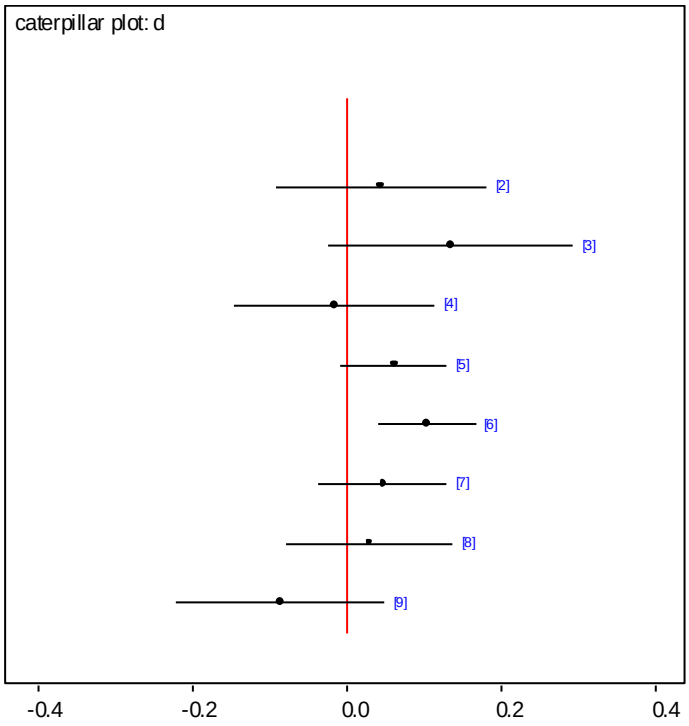

Figure 6 RE model: plot of mean differences of all treatments relative to treatmet 1. Values to the right of the horizontal (red) line favour treatment 1. Treatment codes are given in Table 1.