Chapter 3 Prior Distributions and Evidence Synthesis

3.1 Constructing Prior Distributions

Objectives

- Discuss different ways to construct subjective prior distributions.
- Discuss the criticisms of eliciting subjective prior distributions.
- Explain the relationships that historical data might have with current observations.
- Analyze a crossover design incorporating historical data.

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Prior Distributions

In clinical trials, the Bayesian approach requires the analyst to do the following:

- explicitly state a reasonable opinion concerning the plausibility of different values of the treatment effect
- turn an informally expressed opinion into a mathematical prior distribution of the parameters
- detail the derivation of the prior from an elicitation process or empirical evidence.

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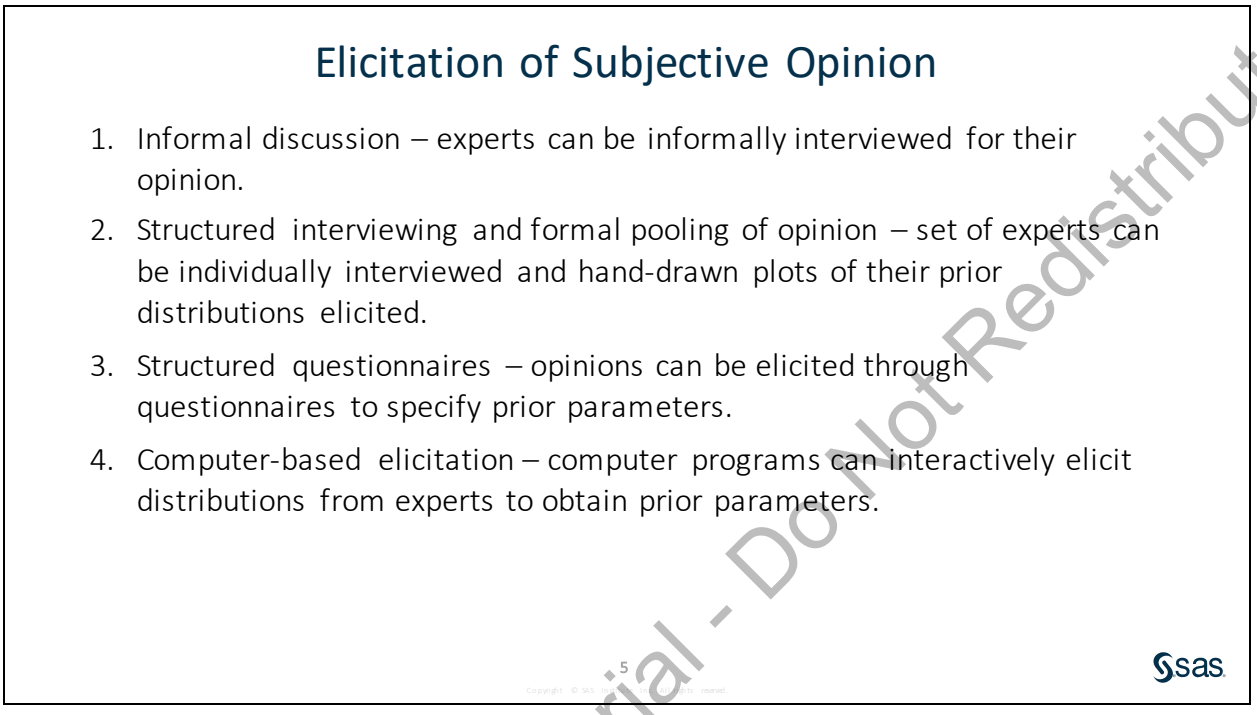
In clinical trials, there might be quantifiable prior beliefs regarding the treatment effect. For example, past studies might show that a new treatment for acute myocardial infarction has the potential to reduce death rates in a hospital by 8% to 10%. However, turning informally expressed opinions into a mathematical prior distribution is perhaps the most difficult aspect of Bayesian analysis.



If the prior distribution is to be generally accepted by a wider community, then there should be some evidential or at least consensus support. However, in some circumstances there might be little objective evidence available and summaries of expert opinion would be indispensable (Spiegelhalter et al. 2004).

Chaloner (1996) provides a review of the methods for prior elicitation in clinical trials. These methods include interviews with clinicians, postal questionnaires, and the use of an interactive computer program to draw a prior distribution. She concludes that fairly simple methods are adequate such as using interactive feedback with a scripted interview, providing experts with a systematic literature review, and basing elicitation on the 2.5^{th} and 97.5^{th} percentiles.

Freedman and Spiegelhalter (1983) describe an interviewing technique where a set of experts was individually interviewed and hand-drawn plots of their prior distributions elicited. Deliberate efforts were made to prevent the opinions from being overconfident. The distributions were then converted to histograms and averaged to produce a prior distribution.

Chaloner and Rhame (2001) used a structured questionnaire to elicit opinions from 59 practicing HIV clinicians concerning baseline rates and potential benefit of two prophylactic treatments. The questionnaire elicited the minimum information to compute a point estimate and a 95% credible interval.

Chaloner et al. (1993) used a computer program that interactively elicited distributions from five clinicians for a trial of prophylactic therapy in AIDS.

Spiegelhalter et al. (2004) feel that extremely detailed elicitation methods in the construction of prior distributions have not yet shown to have any advantage over simple methods. However, they claim that for complex policy problems, which might require substantial subjective input, a more sophisticated approach might be justified.

Elicitation from Multiple Experts

1. Elicit a consensus – a range of techniques exist for bringing diverse opinions into consensus.
2. Calculate a pooled prior – can use arithmetic pooling or logarithmic pooling to compute a pooled prior.
3. Retain the individual priors – the diversity of opinion might be just as important as the average opinion.

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When you are faced with a number of prior distributions elicited from multiple experts, you can elicit a consensus, calculate a pooled prior, or retain the individual priors. One method to compute a pooled prior is *arithmetic pooling*, which takes the average of the height of the prior densities for each parameter value. This has the property that pooled probabilities for any event, such as tail areas, are also averages of the individually assessed tail areas. Another method is *logarithmic pooling*, which takes the average of the logarithms of the density. This has the property that the same pooled posterior distribution is achieved, whether the pooling is done before or after the common likelihood is taken into account.

Problems with Prior Elicitation

1. Subjects are biased in their opinions – experts participating in the trial probably expect the new treatment to be beneficial.
2. The choice of subject biases the results – the choice of experts are not a random sample and might give biased results.
3. Timing of elicitation has an influence – opinions are likely to be biased by what evidence has recently been presented.

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Constructing prior distributions through the elicitation of subjective opinions has been problematic, mainly because people are not good probability assessors. Altman (1994) warns that investigators might even begin to exaggerate their prior beliefs in order to make their prospective trial appear more attractive. Fisher (1996) believes the effort put into elicitation is misplaced because the measured beliefs are likely to be based more on emotion than on scientific evidence.

In clinical trials, the selection of trial investigators to elicit their opinions is not a random sample of well-informed clinicians and might give biased conclusions. A detailed case study by Fayers et al. (2000) showed there is clear over-optimism of investigators. Lewis (1994) even suggests that statisticians reviewing the literature might provide much better prior distributions than clinicians.

The timing of the elicitation even has an effect as Hughes (1991) shows that opinions are likely to be biased by what evidence has recently been presented and by whom.

Potential Biases of Experts

1. Availability – easily recalled events are given higher probability.
2. Adjustment and anchoring – initial assessments tend to exert an inertia.
3. Overconfidence – distributions are too tight.
4. Conjunction fallacy – a higher probability can be given to an event that is a subset of an event with a lower probability.
5. Hindsight bias – if the prior is assessed after seeing the data, the expert might be biased.

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The variety of biases that people suffer when providing their subjective opinions are summarized by Kadane and Wolfson (1997) in the above slide. These concerns have led to a call for more attention to be paid to empirical evidence from past trials, possibly represented as priors expressing a degree of skepticism concerning large effects. Spiegelhalter et al. (2004) believes that elicited priors from investigators show predictable positive bias and should be supplemented, if not replaced, by priors that are either based on evidence or reflect views of skepticism.

Note: The conjunction fallacy occurs when it is assumed that specific conditions are more probable than a single general one. For two events *A* and *B*, $\Pr(A \wedge B) \leq \Pr(A)$ and $\Pr(A \wedge B) \leq \Pr(B)$. Giving (A^B) a higher probability than (A) or (B) would be a conjunction fallacy.

Use of Historical Data

1. Irrelevance – historical data provide no relevant information.
2. Exchangeable – current and past studies are similar and parameters are considered exchangeable.
3. Potential biases – past studies are biased and potential bias can be modeled.
4. Equal but discounted – past studies are unbiased but their precision is decreased.
5. Functional dependence – current parameter of interest is a logical function of parameters estimated in historical studies.
6. Equal – past data can be directly pooled.

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If the results or data of previous similar studies are available, then they should be used in the construction of the prior distributions. The types of possible relationships between the historical parameters and the current parameters of interest documented by Spiegelhalter et al. (2004) are shown in the above slide.

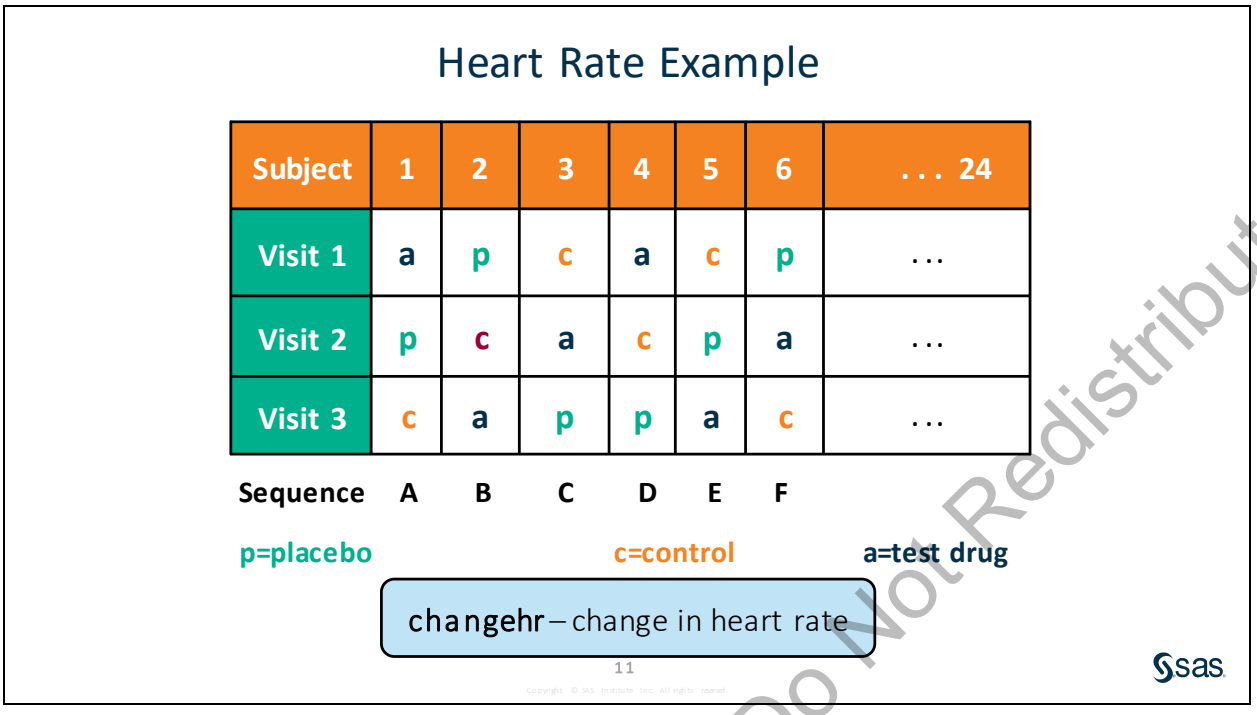
Exchangeability is a strong assumption, but if it is reasonable then you can use databases to provide prior distributions. This leads to a direct use of a meta-analysis of many previous studies, which is discussed in the next section.

If the past studies are biased, then you should make one of the following assumptions:

1. The value of the bias is known.
2. The bias has a known distribution with a mean of 0.
3. The bias is in one direction, so the known distribution has a nonzero mean.

If the previous studies are not directly related to the one in question, you might want to discount their influence. An example of this method is from Greenhouse and Wasserman (1995) where they downweighted a previous trial with 176 subjects to be equivalent to only 10 subjects.

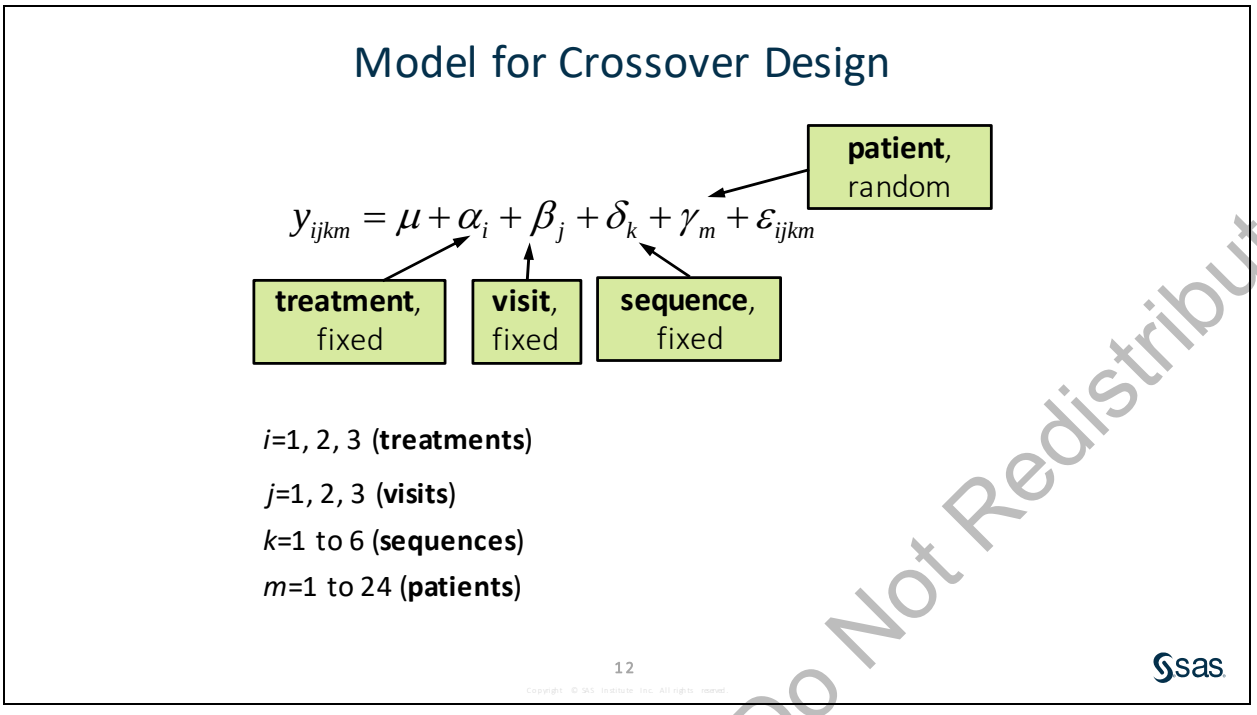
If the past studies have all been measuring identical parameters, then you can directly pool the past data with the current study. However, you are making the strong assumption of exchangeability of individual patients.



Example: A pharmaceutical company conducted a clinical trial to assess the effects of three treatments on the heart rate of patients. The treatments were placebo (**p**), control (**c**), and the test drug (**a**). Each patient in the study received the three treatments in a random order during a time period that was separated from the others so that one treatment did not influence the heart rate measurement obtained after administering the other treatment (in other words, to rule out carry-over effect). Each period was a visit to the clinic. The sequences of administering the treatments were A(**a p c**), B(**p c a**), C(**c a p**), D(**a c p**), E(**c p a**), and F(**p a c**). The drugs were assigned to twenty-four patients in a three-period crossover design, with four patients for each sequence. The change in heart rate at one hour following the treatment was measured.

The data are stored in a SAS data set **sasuser.crossover**. The following variables are in the data set:

patient	patient (subject) ID
sequence	the sequence that the drugs were administered to each patient
visit	the visit to the clinic
drug	the drugs under investigation
changehr	the change in the heart rate between one hour following the treatment and the baseline measurement



Questions asked in a crossover design are whether there is a treatment effect and what is the variability due to the random selection of the patients. You can analyze the data using the above model.

y_{ijkm} the change in the heart rate for the m^{th} patient assigned to the i^{th} drug in the j^{th} period using the k^{th} sequence

μ the overall mean

α_i the effect of the i^{th} drug, a fixed effect

β_j the effect of the j^{th} visit, a fixed effect

δ_k the effect of the k^{th} sequence, a fixed effect

γ_m the effect of the m^{th} patient, assumed i.i.d. N(0, σ^2_γ), thus a random effect

ε_{ijkm} random error, assumed i.i.d. N(0, σ^2_T)

Assume γ_m and ε_{ijkm} are independently distributed random variables.

PROC MIXED Code

```
proc mixed data=sasuser.crossover;
   class patient sequence visit drug;
   model changehr=drug visit sequence /
         ddfm=kr solution;
   random patient;
   title "Crossover Model for Heart Rate Data";
run;
```

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The crossover design data can be analyzed with the PROC MIXED program shown above. The variables sequence, visit, and drug are all fixed effects. However, patient is considered to be a random effect because the patients were randomly selected from a population of patients.

The output from the Covariance Estimates table and the Parameter Estimates table is shown below.

Covariance Parameter Estimates

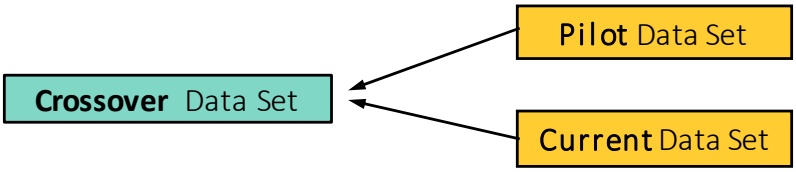
Cov Parm	Estimate
patient	3.1409
Residual	90.5404

Solution for Fixed Effects

Effect	sequence	visit	drug	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept				-7.3889	3.6552	40.3	-2.02	0.0499
drug			a	0.2500	2.7468	44	0.09	0.9279
drug			c	4.3333	2.7468	44	1.58	0.1218
drug			p	0	.	.	.	.
visit		2		-4.3333	2.7468	44	-1.58	0.1218
visit		3		-1.5833	2.7468	44	-0.58	0.5673
visit		4		0	.	.	.	.
sequence	A			1.8333	4.0817	18	0.45	0.6587
sequence	B			6.1667	4.0817	18	1.51	0.1482
sequence	C			-0.6667	4.0817	18	-0.16	0.8721
sequence	D			4.5000	4.0817	18	1.10	0.2848
sequence	E			2.8333	4.0817	18	0.69	0.4964
sequence	F			0	.	.	.	.

Notice only 10 parameters are needed for this model.

Incorporation of Historical Data



patient	sequence	visit	drug	changehr	group
201	B	2	p	-8	current
201	B	3	c	12	current
201	B	4	a	4	current
218	A	2	a	4	pilot
218	A	3	p	-4	pilot
218	A	4	c	8	pilot

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In this example, suppose there was a historical pilot trial data set from a similar crossover design. In Bayesian analysis, you might want to combine the two data sets and create a group indicator variable identifying current versus pilot data. Then use a discounting parameter that reflects your belief on how much weight should be put on the previous analysis.

Power Prior

- If you want to use previous studies but discount their influence, you can use the power prior.
- If you assume that $\theta_h = \theta$, you can discount the historical evidence by taking its likelihood $p(y_h \mid \theta_h)$ to a power a_0.
- a_0 is a discounting parameter constrained from 0 to 1, where 0 corresponds to no incorporation of the historical data while 1 corresponds to including the past evidence in its totality and at face value.

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If you want to discount the influence of the historical data, Ibrahim and Chen (2000) suggest using the power prior. With this prior you assume that the historical parameter is equal to the current

parameter, but you discount the historical evidence by taking the likelihood to a power equal to the discounting parameter. It should be noted that Eddy et al. (1992) are very strong in their criticism of this method, claiming it has no operational interpretation and hence no means of assessing a suitable value for the discounting parameter.

3.02 Multiple Choice Poll

Which bias is the least likely to occur when soliciting experts regarding the derivation of an informative prior?

a. A positive bias where the experts expect the effect to be beneficial.

b. A bias toward no effect where the experts expect the effect to show no impact on the outcome.

c. Selection bias because the choice of experts is not a random sample.

d. Hindsight bias where the experts are biased by what data they have recently seen.

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Incorporation of Historical Data

Example: Fit a general linear mixed model in PROC MCMC for the crossover design data set. First create new variables called **drugalpha** (with values 1 through 3 corresponding to drug **a**, **c**, and **p**), **visitbeta** (with values 1 through 3 corresponding to visit 2, 3, and 4), and **seqdelta** (with values 1 through 6 corresponding to sequence **A** through **F**). In PROC MCMC, request all the diagnostics and the DIC criterion, specify the conjugate gradient optimization, set the number of burn in iterations to 10,000, set the number of iterations in each proposal tuning phase to 10,000, set the number of iterations in the main simulation loop to 500,000, and set the thinning rate to 15. Use ARRAY statements to define the fixed effects for **drug**, the fixed effects for **visit**, and the fixed effects for **sequence.** Define gamma as a random effect with a normal prior distribution (mean of 0 and variance of s2g) and use the power prior to incorporate the pilot data. Set the discounting factor to 0.5 and use the IF statement to assign the appropriate likelihood function to different observations in the data set. Do not specify **beta3** and **delta6** in the PARMS or PRIOR statements and assign a value of 0 to each of these parameters. Also, use the monitor option to monitor the parameters of interest and use the NAMESUFFIX=POSITION option in the RANDOM statement to construct the random effect parameter names using the position number.

```
/* stbay03d01.sas */
data crossover;
   set sasuser.crossover;
   if drug='a' then drugalpha=1;
   if drug='c' then drugalpha=2;
   if drug='p' then drugalpha=3;
   visitbeta=visit-1;
   if sequence='A' then seqdelta=1;
   if sequence='B' then seqdelta=2;
   if sequence='C' then seqdelta=3;
   if sequence='D' then seqdelta=4;
   if sequence='E' then seqdelta=5;
   if sequence='F' then seqdelta=6;
run;
```

Because PROC MCMC does not have a CLASS statement, the categorical variables for the fixed effects will be used in an ARRAY statement with its values corresponding to the elements in the array.

```
proc mcmc data=crossover seed=27513 diag=all dic mchistory=brief
     propcov=congra nbi=5000 ntu=5000 nmc=500000 thin=15 stats=all
     plots(smooth)=all monitor=(alpha beta delta s2t s2g);
   array alpha[3];
   array beta[3];
   array delta[6];
   parms alpha: 0;
   parms beta1 beta2 0;
   parms delta1 delta2 delta3 delta4 delta5 0;
   parms s2t 1;
   parms s2g 1;
   prior alpha: ~ normal(0, var=100);
   prior beta1 beta2 ~ normal(0, var=100);
   prior delta1 delta2 delta3 delta4 delta5 ~ normal(0, var=100);
   prior s2: ~ igamma(2.001, scale=1.001);
   a0=0.5;
   beta[3]=0;
   delta[6]=0;
   random gamma ~ normal(0,var=s2g) subject=patient
          monitor=(gamma) namesuffix=position;
   mu=alpha[drugalpha]+beta[visitbeta]+delta[seqdelta]+gamma;
   llike=logpdf("normal",changehr,mu,s2t);
   if (group="pilot") then llike=a0*llike;
   model general(llike);
   title "Bayesian Analysis of Crossover Design Data";
run;
```

Recall that the power prior enables you to retain information from a historical data set and use it as a prior distribution in the current analysis. The parameter **a0** is a discounting parameter constrained to be between 0 and 1 where 0 corresponds to no incorporation of the historical data and 1 corresponds to full incorporation of the data.

The crossover data set is a combination of the pilot data and the current data. If the data are from the current study, the likelihood function is from a normal distribution. If the data are from the pilot study, the likelihood function is from a weighted normal distribution. The LOGPDF functions returns the logarithm of the normal probability density function. Because the general function is used in the MODEL statement to model the mixture distribution, the logarithm of the likelihood function must be used.

Partial Output

```
                    Bayesian Analysis of Crossover Design Data

                     Number of Observations Read          72
                     Number of Observations Used          72

                                  Parameters

                      Sampling         Initial
Block    Parameter    Method             Value    Prior Distribution

    1    alpha1       N-Metropolis           0    normal(0, var = 100)
         alpha2                              0    normal(0, var = 100)
         alpha3                              0    normal(0, var = 100)
    2    beta1        N-Metropolis           0    normal(0, var = 100)
         beta2                               0    normal(0, var = 100)
```

```
          3    delta1        N-Metropolis           0    normal(0, var = 100)
               delta2                               0    normal(0, var = 100)
               delta3                               0    normal(0, var = 100)
               delta4                               0    normal(0, var = 100)
               delta5                               0    normal(0, var = 100)
          4    s2t           N-Metropolis      1.0000    igamma(2.001, scale = 1.001)
          5    s2g           Conjugate         1.0000    igamma(2.001, scale = 1.001)

                                  Random Effect Parameters

           Sampling              Number of   Subject                  Prior
Parameter  Method        Subject  Subjects   Values                   Distribution

gamma      N-Metropolis  patient        24   1 2 3 4 5 6 7 8 9 10 11  normal(0,var=s2g)
                                           12 13 14 15 16 17 18 19
                                           20 ...
```

The alpha parameters deal with the fixed drug effect, the beta parameters deal with the fixed visit effect, the delta parameters deal with the fixed sequence effect, and the gamma parameters deal with the random patient effect. Notice the absence of **beta3** and **delta6**.

Conjugate sampling was used to estimate the variance of the random effects, but the default sampling algorithm, which is a random walk Metropolis based on a normal kernel, was used to estimate the total variance. PROC MCMC cannot detect conjugacy on the total variance of the likelihood function because of the complexity of the design of the MODEL statement.

```
                                  Tuning History

                                RWM Scale       RWM Acceptance Rate
                          Phase      Low      High      Low      High

                              1    2.380     2.380    0.371    0.813
                              2    3.164     11.99    0.222    0.338
                              3    3.185     14.88    0.228    0.316
                              4    3.185     14.88    0.215    0.334
                              5    3.281     14.88    0.209    0.292

                                  Burn-In History

                                RWM Scale       RWM Acceptance Rate
                               Low      High      Low      High

                             3.281    14.88    0.221    0.293

                                  Sampling History

                                RWM Scale       RWM Acceptance Rate
                               Low      High      Low      High

                             3.281    14.88    0.219    0.290

                                Posterior Summaries

                                             Standard                Percentiles
      Parameter            N        Mean     Deviation          25          50          75

      alpha1           33334     -5.8723        3.1984     -7.9890     -5.8862     -3.7371
      alpha2           33334     -0.8889        3.2097     -3.0285     -0.8860      1.2355
```

alpha3	33334	-5.1002	3.2405	-7.2637	-5.1211	-2.9536
beta1	33334	-4.8211	2.7896	-6.7007	-4.8235	-2.9532
beta2	33334	-1.6710	2.8011	-3.5586	-1.6817	0.2084
beta3	33334	0	0	0	0	0
delta1	33334	-1.0047	3.6161	-3.4437	-0.9968	1.4070
delta2	33334	5.2752	3.6354	2.8334	5.2836	7.7286
delta3	33334	-3.5547	3.7493	-6.0758	-3.5932	-1.0319
delta4	33334	2.7164	3.6250	0.2897	2.7382	5.1712
delta5	33334	-0.0336	3.6336	-2.4761	-0.0704	2.3979
delta6	33334	0	0	0	0	0
s2t	33334	9.5750	0.9465	8.9057	9.4995	10.1661
s2g	33334	0.8869	1.1498	0.3661	0.5837	0.9808
gamma_1	33334	0.0916	0.9128	-0.4275	0.0705	0.5829
gamma_2	33334	0.0944	0.9270	-0.4412	0.0692	0.5964
gamma_3	33334	0.0241	0.9113	-0.4938	0.0194	0.5283
gamma_4	33334	0.1356	0.9386	-0.4032	0.0954	0.6212
gamma_5	33334	-0.2095	0.9583	-0.6923	-0.1463	0.3555
gamma_6	33334	0.1699	0.9417	-0.3751	0.1216	0.6594
gamma_7	33334	-0.1436	0.9356	-0.6325	-0.1039	0.3904
gamma_8	33334	0.0181	0.9144	-0.4979	0.0130	0.5262
gamma_9	33334	-0.0867	0.9313	-0.5847	-0.0630	0.4373
gamma_10	33334	0.00875	0.9170	-0.5040	0.0145	0.5227
gamma_11	33334	-0.1101	0.9302	-0.5985	-0.0825	0.4287
gamma_12	33334	-0.0836	0.9248	-0.5818	-0.0615	0.4384
gamma_13	33334	0.000452	0.9195	-0.5176	-0.00286	0.5121
gamma_14	33334	-0.1286	0.9259	-0.6234	-0.1002	0.4091
gamma_15	33334	-0.0285	0.9223	-0.5365	-0.0208	0.4823
gamma_16	33334	-0.0813	0.9242	-0.5829	-0.0594	0.4463
gamma_17	33334	0.1440	0.9335	-0.3953	0.1127	0.6399
gamma_18	33334	0.1389	0.9495	-0.4054	0.1042	0.6325
gamma_19	33334	0.000453	0.9283	-0.5189	-0.00578	0.5134
gamma_20	33334	-0.1365	0.9490	-0.6288	-0.0953	0.4093
gamma_21	33334	0.1270	0.9384	-0.4149	0.0952	0.6221
gamma_22	33334	0.0361	0.9347	-0.4797	0.0263	0.5428
gamma_23	33334	-0.0571	0.9268	-0.5605	-0.0399	0.4586
gamma_24	33334	-0.0206	0.9313	-0.5267	-0.0194	0.4906

Posterior Intervals

Parameter	Alpha	Equal-Tail Interval		HPD Interval	
alpha1	0.050	-12.1549	0.4368	-12.1507	0.4370
alpha2	0.050	-7.2257	5.4706	-7.3649	5.3146
alpha3	0.050	-11.4305	1.2241	-11.4464	1.2031
beta1	0.050	-10.2815	0.6693	-10.2208	0.7101
beta2	0.050	-7.1548	3.8051	-7.1657	3.7788
beta3	0.050	0	0	0	0
delta1	0.050	-8.1176	6.0813	-7.9965	6.1784
delta2	0.050	-1.8837	12.3927	-1.7456	12.4947
delta3	0.050	-10.8846	3.8236	-10.9559	3.7178
delta4	0.050	-4.4612	9.7748	-4.4709	9.7533
delta5	0.050	-7.1062	7.1163	-7.2142	6.9903
delta6	0.050	0	0	0	0
s2t	0.050	7.9344	11.6440	7.8422	11.4894
s2g	0.050	0.1816	3.4983	0.1038	2.4784
gamma_1	0.050	-1.6666	1.9987	-1.6755	1.9861
gamma_2	0.050	-1.6910	2.0241	-1.7203	1.9895

gamma_3	0.050	-1.7970	1.8722	-1.8077	1.8600
gamma_4	0.050	-1.6218	2.1315	-1.6988	2.0318
gamma_5	0.050	-2.3078	1.4905	-2.0903	1.6423
gamma_6	0.050	-1.5666	2.1822	-1.5792	2.1578
gamma_7	0.050	-2.1574	1.6352	-2.0457	1.7244
gamma_8	0.050	-1.8364	1.8654	-1.7654	1.9323
gamma_9	0.050	-2.0308	1.7033	-1.9335	1.7707
gamma_10	0.050	-1.8279	1.8589	-1.8545	1.8225
gamma_11	0.050	-2.0777	1.6610	-1.9688	1.7617
gamma_12	0.050	-1.9964	1.7045	-1.9725	1.7220
gamma_13	0.050	-1.8502	1.8533	-1.8522	1.8485
gamma_14	0.050	-2.0875	1.6301	-2.0084	1.6914
gamma_15	0.050	-1.9099	1.8172	-1.7910	1.9119
gamma_16	0.050	-2.0293	1.7136	-1.9842	1.7395
gamma_17	0.050	-1.6067	2.1206	-1.6478	2.0713
gamma_18	0.050	-1.6323	2.1635	-1.7079	2.0686
gamma_19	0.050	-1.8722	1.8621	-1.8584	1.8734
gamma_20	0.050	-2.1604	1.6404	-2.0264	1.7413
gamma_21	0.050	-1.6294	2.1319	-1.7883	1.9324
gamma_22	0.050	-1.8255	1.9312	-1.8565	1.8958
gamma_23	0.050	-1.9399	1.7598	-1.9248	1.7708
gamma_24	0.050	-1.8993	1.8171	-1.8944	1.8200

The model results show none of the fixed effect parameters have a large proportion of values greater than or less than zero. In fact, zero is in every posterior interval. Notice **beta3** and **delta6** have a value of 0. Notice that several random effect terms have relatively small means with large standard deviations, which might affect the Heidelberger-Welch half-width test.

Monte Carlo Standard Errors

Parameter	MCSE	Standard Deviation	MCSE/SD
alpha1	0.0317	3.1984	0.00991
alpha2	0.0315	3.2097	0.00982
alpha3	0.0322	3.2405	0.00994
beta1	0.0199	2.7896	0.00715
beta2	0.0202	2.8011	0.00723
beta3	0	0	.
delta1	0.0318	3.6161	0.00880
delta2	0.0331	3.6354	0.00910
delta3	0.0326	3.7493	0.00869
delta4	0.0333	3.6250	0.00918
delta5	0.0327	3.6336	0.00899
delta6	0	0	.
s2t	0.00564	0.9465	0.00595
s2g	0.0124	1.1498	0.0108
gamma_1	0.00512	0.9128	0.00561
gamma_2	0.00523	0.9270	0.00564
gamma_3	0.00510	0.9113	0.00560
gamma_4	0.00541	0.9386	0.00576
gamma_5	0.00599	0.9583	0.00625
gamma_6	0.00558	0.9417	0.00593
gamma_7	0.00534	0.9356	0.00570
gamma_8	0.00501	0.9144	0.00548
gamma_9	0.00510	0.9313	0.00548
gamma_10	0.00502	0.9170	0.00548
gamma_11	0.00530	0.9302	0.00570

gamma_12	0.00521	0.9248	0.00563
gamma_13	0.00509	0.9195	0.00554
gamma_14	0.00521	0.9259	0.00563
gamma_15	0.00511	0.9223	0.00554
gamma_16	0.00516	0.9242	0.00558
gamma_17	0.00535	0.9335	0.00573
gamma_18	0.00554	0.9495	0.00583
gamma_19	0.00515	0.9283	0.00555
gamma_20	0.00543	0.9490	0.00572
gamma_21	0.00540	0.9384	0.00576
gamma_22	0.00512	0.9347	0.00548
gamma_23	0.00523	0.9268	0.00564
gamma_24	0.00510	0.9313	0.00548

The Monte Carlo Standard Errors table indicates that the standard errors of the mean estimates for each of the parameters are relatively small, with respect to the posterior standard deviations. The values in the MCSE/SD column (ratios of the standard errors and the standard deviations) are small, which means that only a fraction of the posterior variability is due to the simulation.

Posterior Autocorrelations

Parameter	Lag 1	Lag 5	Lag 10	Lag 50
alpha1	0.4482	0.0586	0.0153	-0.0031
alpha2	0.4662	0.0593	-0.0009	0.0000
alpha3	0.4695	0.0665	-0.0030	0.0036
beta1	0.2302	-0.0017	-0.0100	0.0052
beta2	0.2337	0.0130	-0.0036	0.0092
beta3	.	.	.	.
delta1	0.4080	0.0287	0.0083	-0.0062
delta2	0.4156	0.0355	0.0109	-0.0086
delta3	0.3813	0.0249	0.0064	-0.0057
delta4	0.4313	0.0391	-0.0003	-0.0006
delta5	0.4122	0.0297	0.0112	0.0010
delta6	.	.	.	.
s2t	0.0726	-0.0023	-0.0065	0.0040
s2g	0.5515	0.0789	0.0177	-0.0103
gamma_1	0.0254	0.0009	-0.0069	-0.0083
gamma_2	0.0309	0.0011	0.0003	-0.0034
gamma_3	0.0221	0.0068	0.0051	0.0005
gamma_4	0.0355	0.0102	-0.0070	0.0072
gamma_5	0.0745	0.0033	-0.0005	0.0012
gamma_6	0.0460	0.0053	0.0080	-0.0008
gamma_7	0.0269	0.0072	0.0110	-0.0073
gamma_8	0.0029	-0.0094	-0.0005	-0.0073
gamma_9	0.0095	-0.0098	0.0025	0.0001
gamma_10	-0.0015	-0.0030	0.0015	0.0028
gamma_11	0.0409	-0.0016	-0.0077	0.0078
gamma_12	0.0290	-0.0053	-0.0021	0.0077
gamma_13	0.0111	0.0023	-0.0013	0.0003
gamma_14	0.0276	-0.0006	-0.0029	-0.0011
gamma_15	0.0113	0.0058	0.0125	-0.0020
gamma_16	0.0190	0.0019	0.0029	-0.0030
gamma_17	0.0334	0.0006	0.0004	0.0033
gamma_18	0.0350	0.0046	0.0033	-0.0012
gamma_19	0.0125	-0.0104	0.0016	-0.0026
gamma_20	0.0270	0.0024	0.0118	-0.0083
gamma_21	0.0407	0.0084	-0.0026	-0.0027

gamma_22	0.0071	-0.0027	-0.0110	-0.0044
gamma_23	0.0162	-0.0001	-0.0032	-0.0050
gamma_24	-0.0013	-0.0041	-0.0113	-0.0064

The Posterior Autocorrelations table shows that the autocorrelations among posterior samples reduce quickly and become almost nonexistent after lag 5.

Geweke Diagnostics

Parameter	z	Pr > |z|
alpha1	-0.1266	0.8993
alpha2	-0.7429	0.4575
alpha3	-0.1686	0.8661
beta1	0.3651	0.7150
beta2	1.2346	0.2170
beta3	.	.
delta1	0.1788	0.8581
delta2	-0.4309	0.6666
delta3	-0.4609	0.6449
delta4	0.0722	0.9425
delta5	0.3638	0.7160
delta6	.	.
s2t	-1.7119	0.0869
s2g	0.4913	0.6232
gamma_1	1.7297	0.0837
gamma_2	1.0053	0.3147
gamma_3	-0.7710	0.4407
gamma_4	1.4306	0.1525
gamma_5	0.0659	0.9475
gamma_6	-0.1505	0.8804
gamma_7	-0.9379	0.3483
gamma_8	0.3872	0.6986
gamma_9	0.1957	0.8448
gamma_10	-1.1583	0.2468
gamma_11	-0.4186	0.6755
gamma_12	-0.5127	0.6082
gamma_13	0.1809	0.8564
gamma_14	-2.3337	0.0196
gamma_15	1.2467	0.2125
gamma_16	0.1664	0.8678
gamma_17	1.9017	0.0572
gamma_18	0.8852	0.3760
gamma_19	-1.4362	0.1510
gamma_20	-0.0490	0.9610
gamma_21	0.1859	0.8525
gamma_22	-0.4466	0.6552
gamma_23	-0.4510	0.6520
gamma_24	0.4249	0.6709

The Geweke Diagnostics table indicates that none of the fixed effect parameters failed the test and only one random effect parameters failed the test (gamma14).

Raftery-Lewis Diagnostics

Quantile=0.025 Accuracy=+/-0.005 Probability=0.95 Epsilon=0.001

	Number of Samples			Dependence
Parameter	Burn-In	Total	Minimum	Factor

alpha1	6	8710	3746	2.3251
alpha2	5	8384	3746	2.2381
alpha3	6	8394	3746	2.2408
beta1	3	4199	3746	1.1209
beta2	3	4272	3746	1.1404
beta3	.	.	3746	.
delta1	4	5126	3746	1.3684
delta2	4	5270	3746	1.4068
delta3	4	4875	3746	1.3014
delta4	4	5075	3746	1.3548
delta5	4	5100	3746	1.3615
delta6	.	.	3746	.
s2t	2	3957	3746	1.0563
s2g	4	4592	3746	1.2258
gamma_1	5	8184	3746	2.1847
gamma_2	3	4097	3746	1.0937
gamma_3	3	4137	3746	1.1044
gamma_4	3	4017	3746	1.0723
gamma_5	5	8703	3746	2.3233
gamma_6	3	4067	3746	1.0857
gamma_7	5	8862	3746	2.3657
gamma_8	3	4027	3746	1.0750
gamma_9	5	8882	3746	2.3711
gamma_10	4	8397	3746	2.2416
gamma_11	4	7911	3746	2.1119
gamma_12	3	4390	3746	1.1719
gamma_13	2	3967	3746	1.0590
gamma_14	5	8103	3746	2.1631
gamma_15	5	8557	3746	2.2843
gamma_16	5	8471	3746	2.2613
gamma_17	2	3986	3746	1.0641
gamma_18	3	4017	3746	1.0723
gamma_19	3	4107	3746	1.0964
gamma_20	5	8585	3746	2.2918
gamma_21	3	4107	3746	1.0964
gamma_22	3	4047	3746	1.0804
gamma_23	5	8267	3746	2.2069
gamma_24	3	4127	3746	1.1017

Heidelberger-Welch Diagnostics

	Stationarity Test				Half-Width Test			
Parameter	Cramer-von Mises Stat	p-Value	Test Outcome	Iterations Discarded	Half-Width	Mean	Relative Half-Width	Test Outcome
alpha1	0.0403	0.9315	Passed	0	0.0691	-5.8723	-0.0118	Passed
alpha2	0.0690	0.7578	Passed	0	0.0645	-0.8889	-0.0725	Passed
alpha3	0.1348	0.4392	Passed	0	0.0615	-5.1002	-0.0121	Passed
beta1	0.0467	0.8962	Passed	0	0.0337	-4.8211	-0.00699	Passed
beta2	0.1647	0.3477	Passed	0	0.0374	-1.6710	-0.0224	Passed
beta3	.	.	Failed	.	.	.	.	
delta1	0.0269	0.9852	Passed	0	0.0693	-1.0047	-0.0690	Passed
delta2	0.0389	0.9389	Passed	0	0.0772	5.2752	0.0146	Passed
delta3	0.1169	0.5080	Passed	0	0.0759	-3.5547	-0.0213	Passed
delta4	0.0325	0.9672	Passed	0	0.0691	2.7164	0.0254	Passed
delta5	0.1411	0.4179	Passed	0	0.0726	-0.0336	-2.1583	Failed
delta6	.	.	Failed	.	.	.	.	

s2t	0.0790	0.6975	Passed	0	0.00979	9.5750	0.00102	Passed
s2g	0.0682	0.7625	Passed	0	0.0215	0.8869	0.0242	Passed
gamma_1	0.1852	0.2981	Passed	0	0.00903	0.0916	0.0986	Passed
gamma_2	0.0541	0.8513	Passed	0	0.0101	0.0944	0.1075	Failed
gamma_3	0.1574	0.3678	Passed	0	0.00883	0.0241	0.3656	Failed
gamma_4	0.2624	0.1732	Passed	0	0.0116	0.1356	0.0853	Passed
gamma_5	0.1846	0.2994	Passed	0	0.0118	-0.2095	-0.0563	Passed
gamma_6	0.1357	0.4362	Passed	0	0.0130	0.1699	0.0763	Passed
gamma_7	0.0596	0.8162	Passed	0	0.00932	-0.1436	-0.0649	Passed
gamma_8	0.0516	0.8668	Passed	0	0.0125	0.0181	0.6908	Failed
gamma_9	0.0988	0.5906	Passed	0	0.00894	-0.0867	-0.1031	Failed
gamma_10	0.1749	0.3218	Passed	0	0.00910	0.00875	1.0395	Failed
gamma_11	0.0675	0.7667	Passed	0	0.0115	-0.1101	-0.1046	Failed
gamma_12	0.0448	0.9070	Passed	0	0.0111	-0.0836	-0.1325	Failed
gamma_13	0.1785	0.3133	Passed	0	0.0107	0.000452	23.6641	Failed
gamma_14	0.2658	0.1693	Passed	0	0.0103	-0.1286	-0.0800	Passed
gamma_15	0.0623	0.7997	Passed	0	0.00932	-0.0285	-0.3267	Failed
gamma_16	0.1186	0.5010	Passed	0	0.00766	-0.0813	-0.0942	Passed
gamma_17	0.3948	0.0746	Passed	3333	0.0105	0.1413	0.0743	Passed
gamma_18	0.3559	0.0948	Passed	0	0.0125	0.1389	0.0898	Passed
gamma_19	0.0923	0.6238	Passed	0	0.0108	0.000453	23.9390	Failed
gamma_20	0.1385	0.4265	Passed	0	0.01000	-0.1365	-0.0733	Passed
gamma_21	0.2187	0.2340	Passed	0	0.0100	0.1270	0.0789	Passed
gamma_22	0.1476	0.3970	Passed	0	0.0107	0.0361	0.2957	Failed
gamma_23	0.0497	0.8784	Passed	0	0.0127	-0.0571	-0.2230	Failed
gamma_24	0.0505	0.8734	Passed	0	0.00872	-0.0206	-0.4243	Failed

Several parameters failed the Heidelberger-Welch half-width test, which indicates that there are not enough data to accurately estimate the mean with 95% confidence under a predetermined accuracy value. As was stated earlier, an implicit assumption is that large means are often accompanied by large variances. If this assumption is not met, then this test can produce false rejections when a small mean around 0 is accompanied by a large standard deviation. The parameters that failed the test did indeed have a relatively large standard deviation and a small mean. As with any diagnostic statistic, it is important to examine the diagnostic plots to see whether there truly is a problem.

Effective Sample Sizes

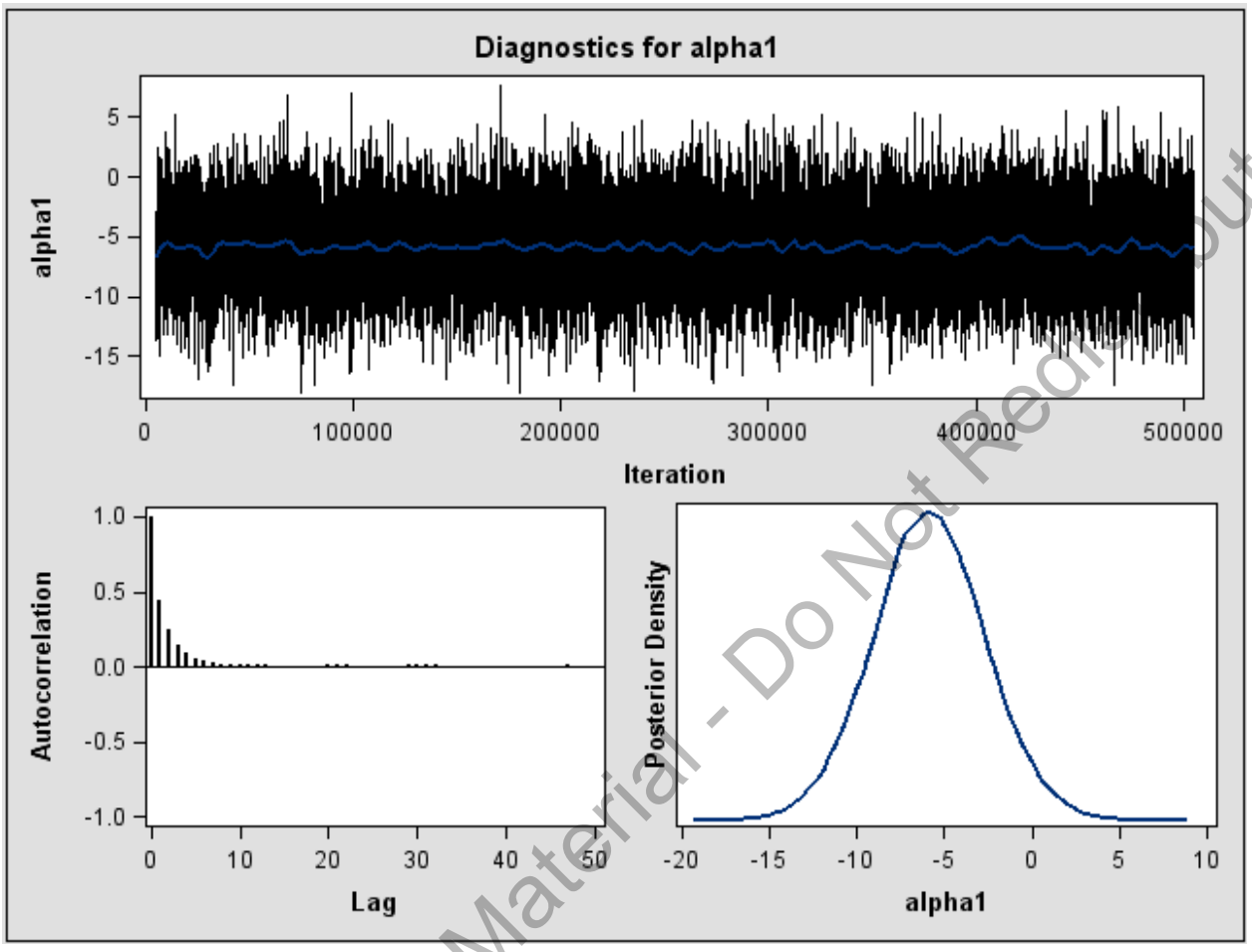
Parameter	ESS	Autocorrelation Time	Efficiency
alpha1	10173.2	3.2767	0.3052
alpha2	10373.7	3.2133	0.3112
alpha3	10111.0	3.2968	0.3033
beta1	19559.1	1.7043	0.5868
beta2	19143.1	1.7413	0.5743
beta3	1.0	33334.0	0.0000
delta1	12903.5	2.5833	0.3871
delta2	12080.2	2.7594	0.3624
delta3	13257.0	2.5144	0.3977
delta4	11868.3	2.8087	0.3560
delta5	12383.9	2.6917	0.3715
delta6	1.0	33334.0	0.0000
s2t	28210.4	1.1816	0.8463
s2g	8593.6	3.8789	0.2578
gamma_1	31721.2	1.0508	0.9516
gamma_2	31392.5	1.0618	0.9418
gamma_3	31924.4	1.0442	0.9577
gamma_4	30152.6	1.1055	0.9046

gamma_5	25606.2	1.3018	0.7682
gamma_6	28447.1	1.1718	0.8534
gamma_7	30747.8	1.0841	0.9224
gamma_8	33334.0	1.0000	1.0000
gamma_9	33334.0	1.0000	1.0000
gamma_10	33334.0	1.0000	1.0000
gamma_11	30812.8	1.0818	0.9244
gamma_12	31504.9	1.0581	0.9451
gamma_13	32609.5	1.0222	0.9783
gamma_14	31591.4	1.0552	0.9477
gamma_15	32596.4	1.0226	0.9779
gamma_16	32113.7	1.0380	0.9634
gamma_17	30426.1	1.0956	0.9128
gamma_18	29405.9	1.1336	0.8822
gamma_19	32519.9	1.0250	0.9756
gamma_20	30573.0	1.0903	0.9172
gamma_21	30143.2	1.1059	0.9043
gamma_22	33334.0	1.0000	1.0000
gamma_23	31447.3	1.0600	0.9434
gamma_24	33334.0	1.0000	1.0000

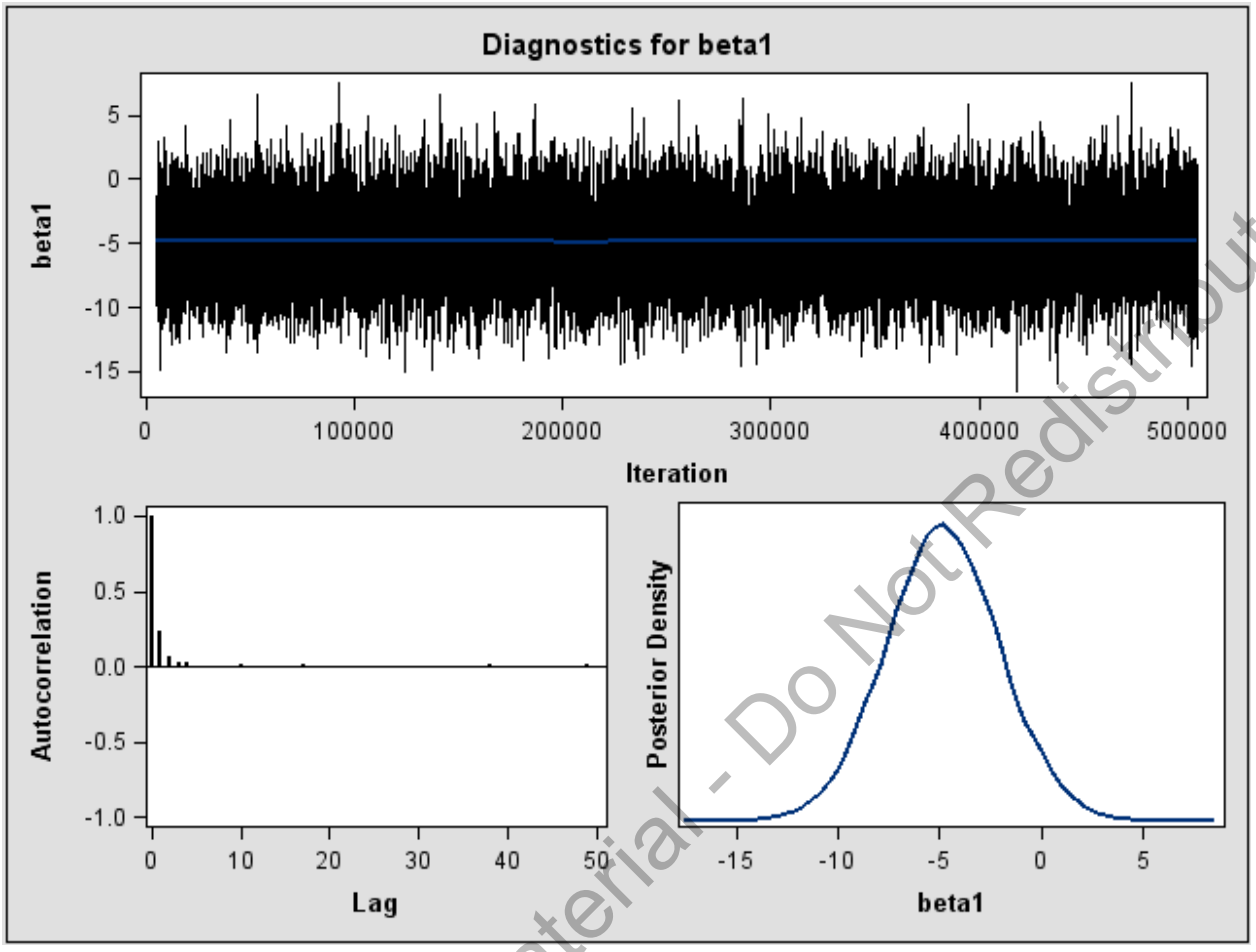
The effective sample sizes indicate no issues.

```
                Deviance Information Criterion

Dbar (posterior mean of deviance)              442.775
Dmean (deviance evaluated at posterior mean)   432.635
pD (effective number of parameters)             10.140
DIC (smaller is better)                        452.915

The GENERAL or DGENERAL function is used in this program.
To make meaningful comparisons, you must ensure that all
GENERAL or DGENERAL functions include appropriate
normalizing constants. Otherwise, DIC comparisons can be
misleading.
```

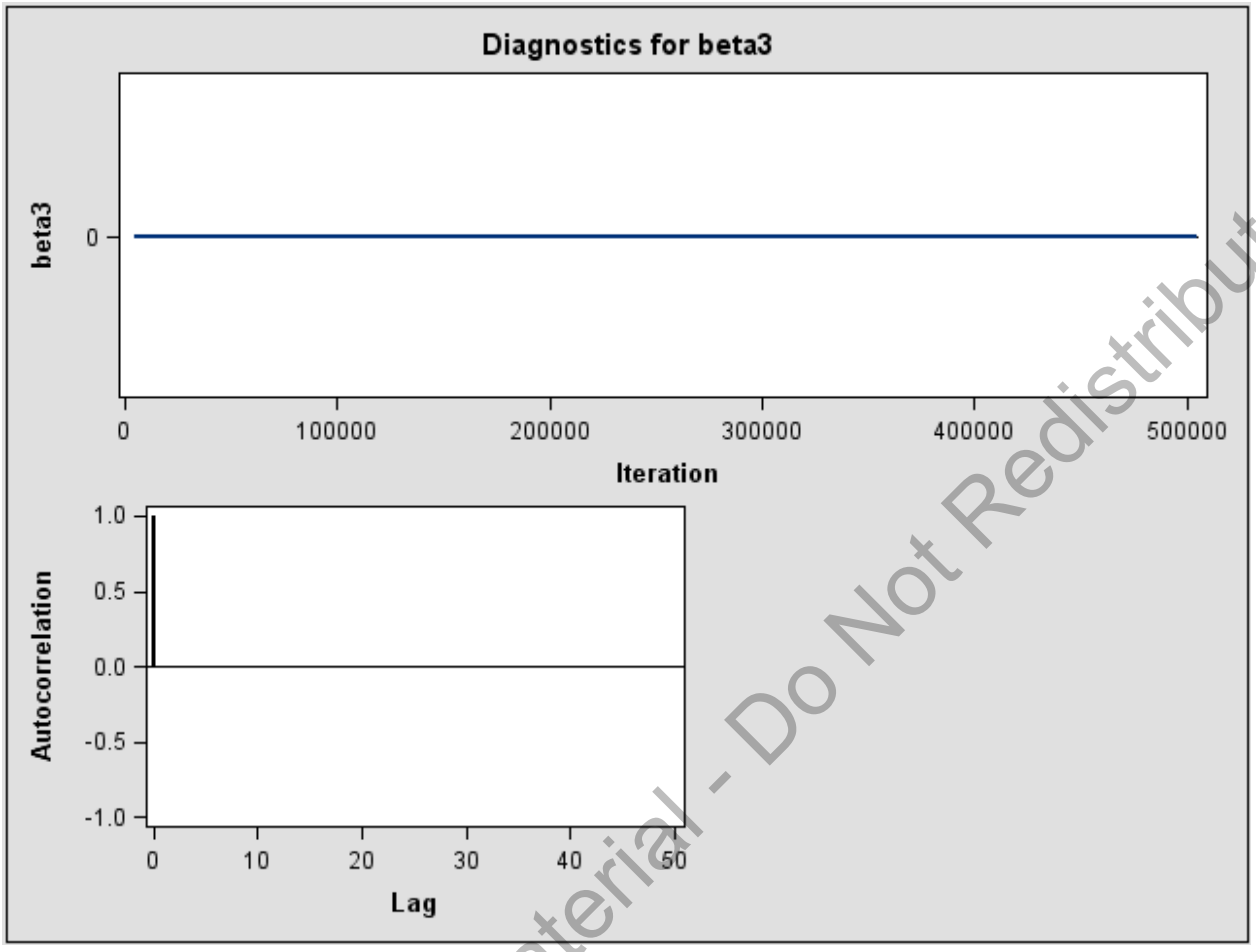
Partial Graphics Output



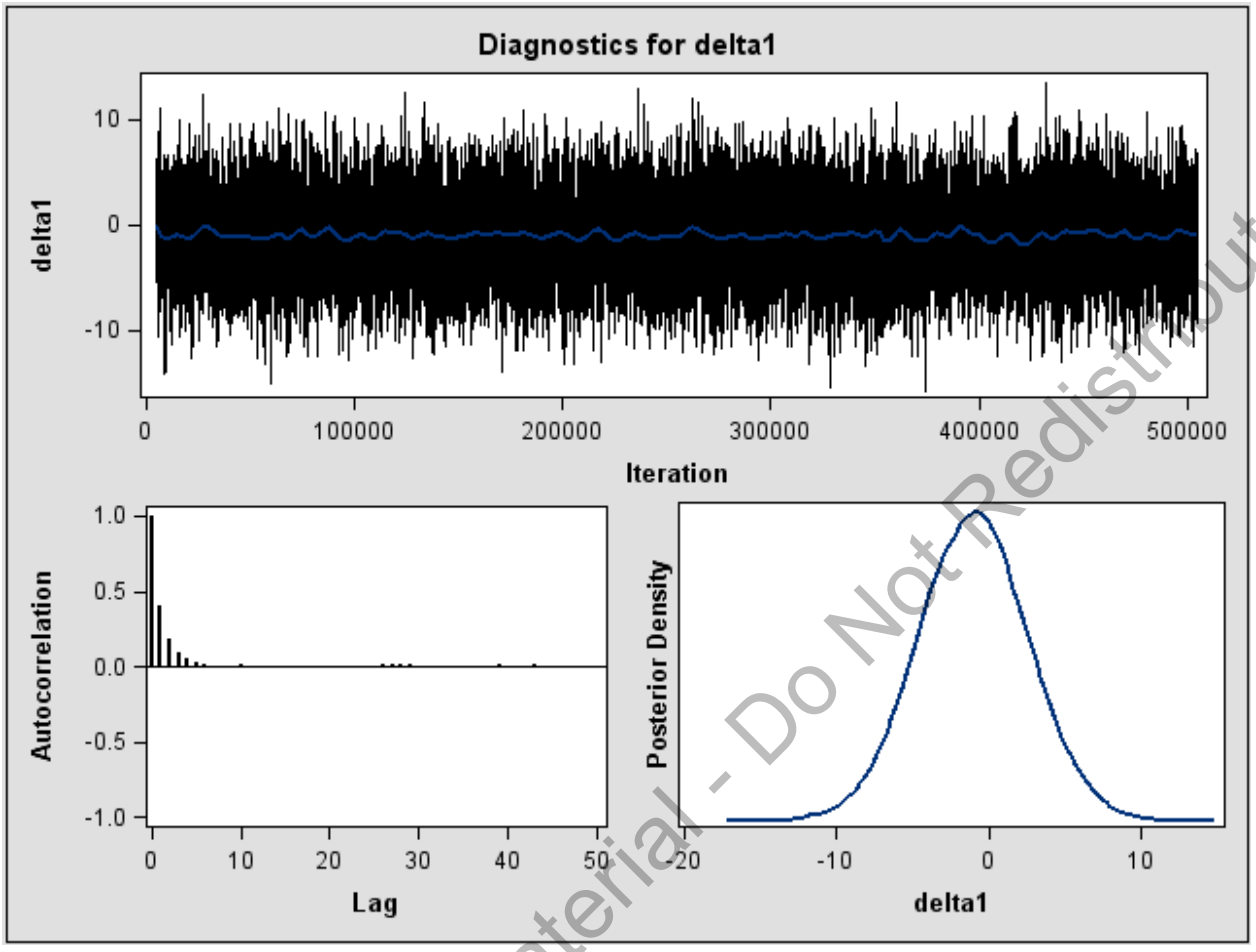
The diagnostic plots for **alpha1** show good Markov chain mixing with small autocorrelations after lag 5.



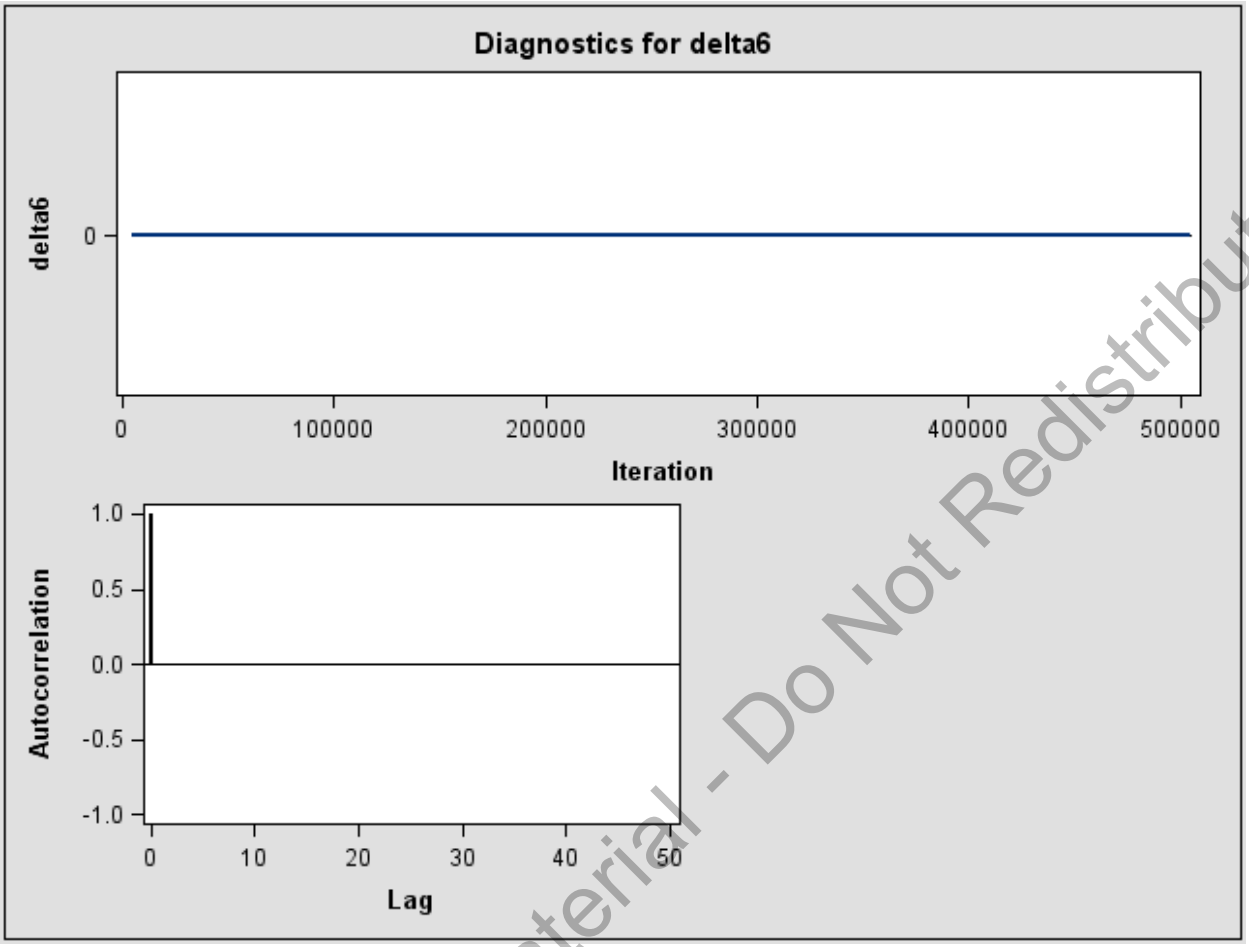
The diagnostic plots for **beta1** show excellent Markov chain mixing with small autocorrelations.



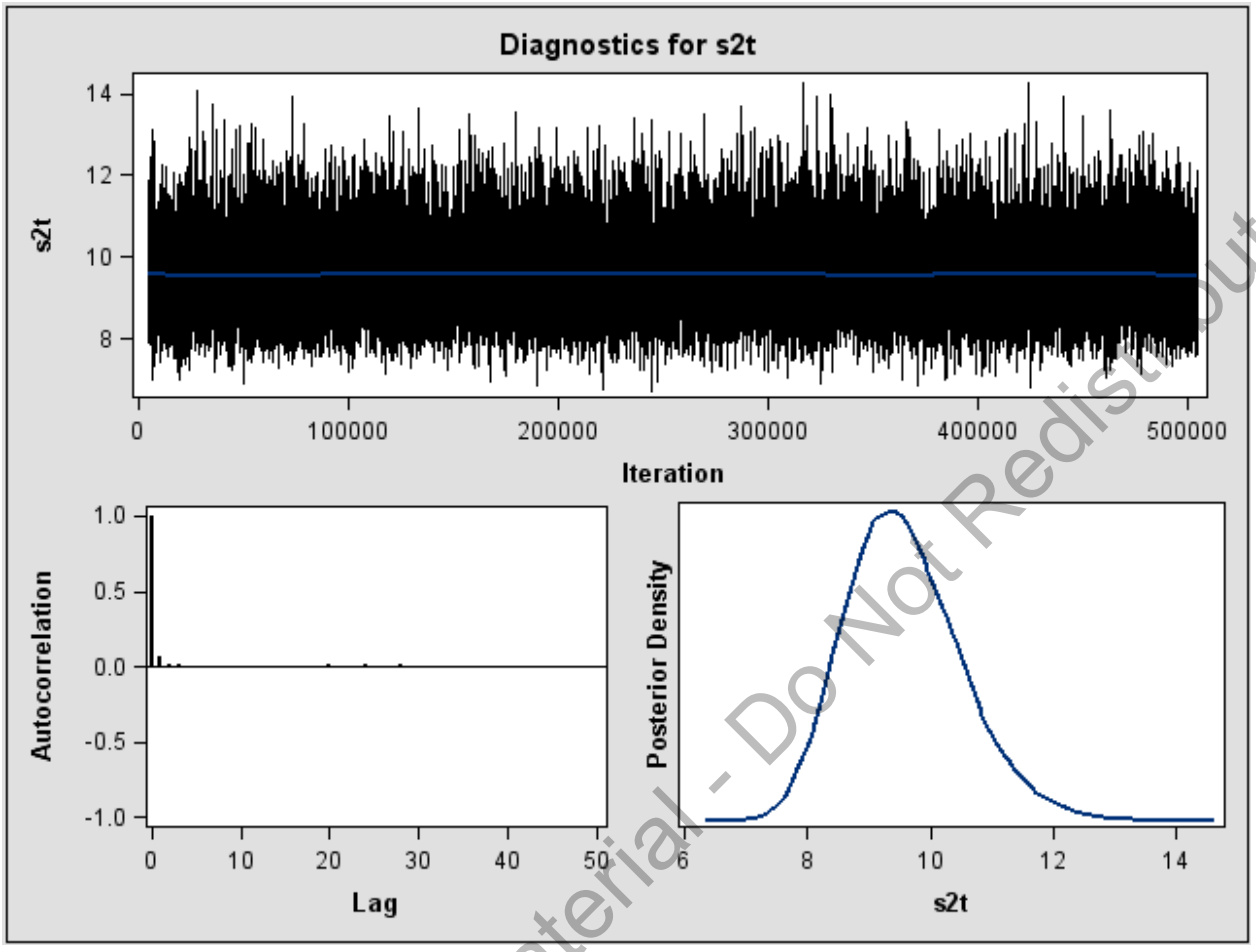
The diagnostic plots for **beta3** show a constant value of 0 (which is expected).



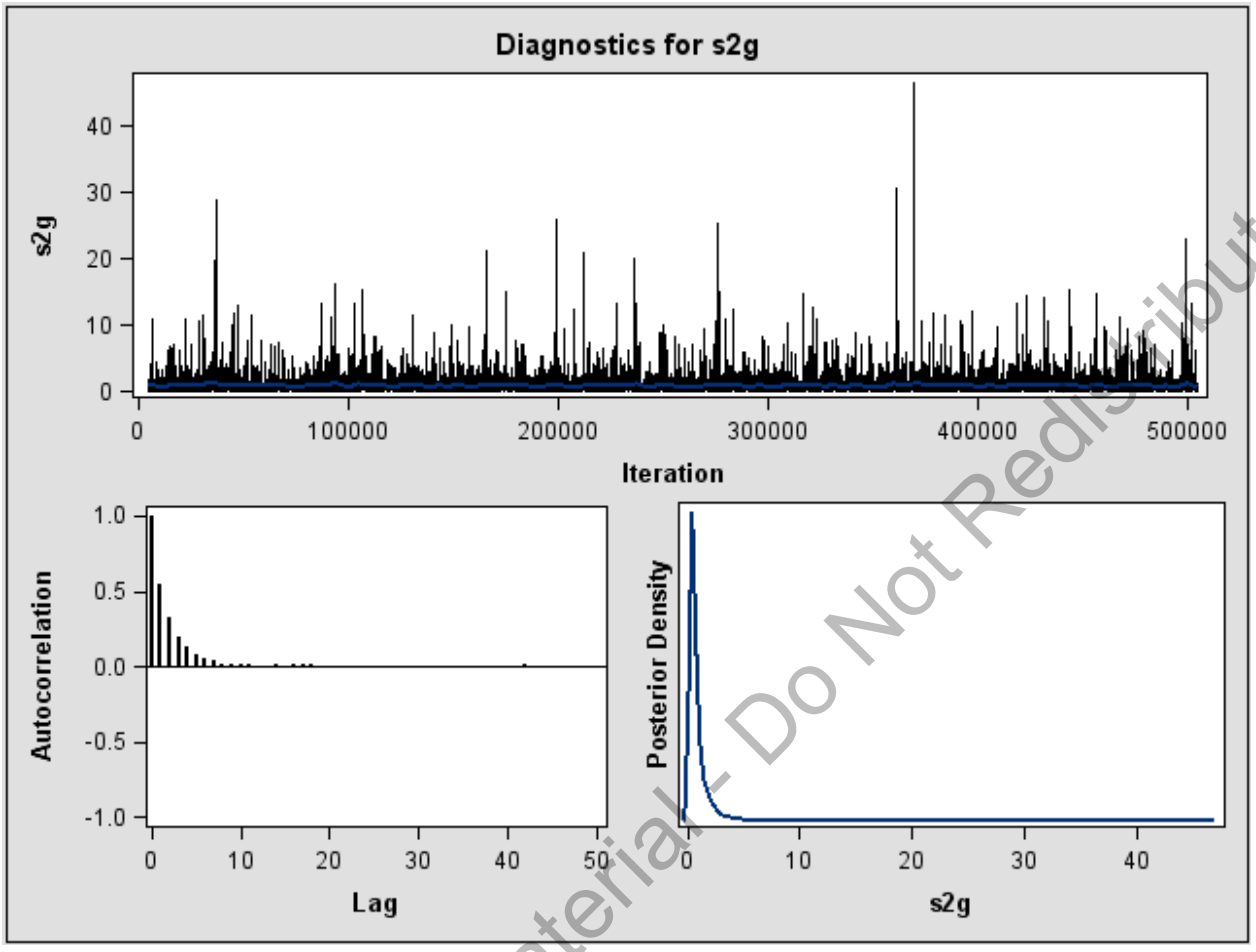
The diagnostic plots for **delta1** show good Markov chain mixing with small autocorrelations after lag 5. Notice the zero value is near the center of the posterior density distribution.



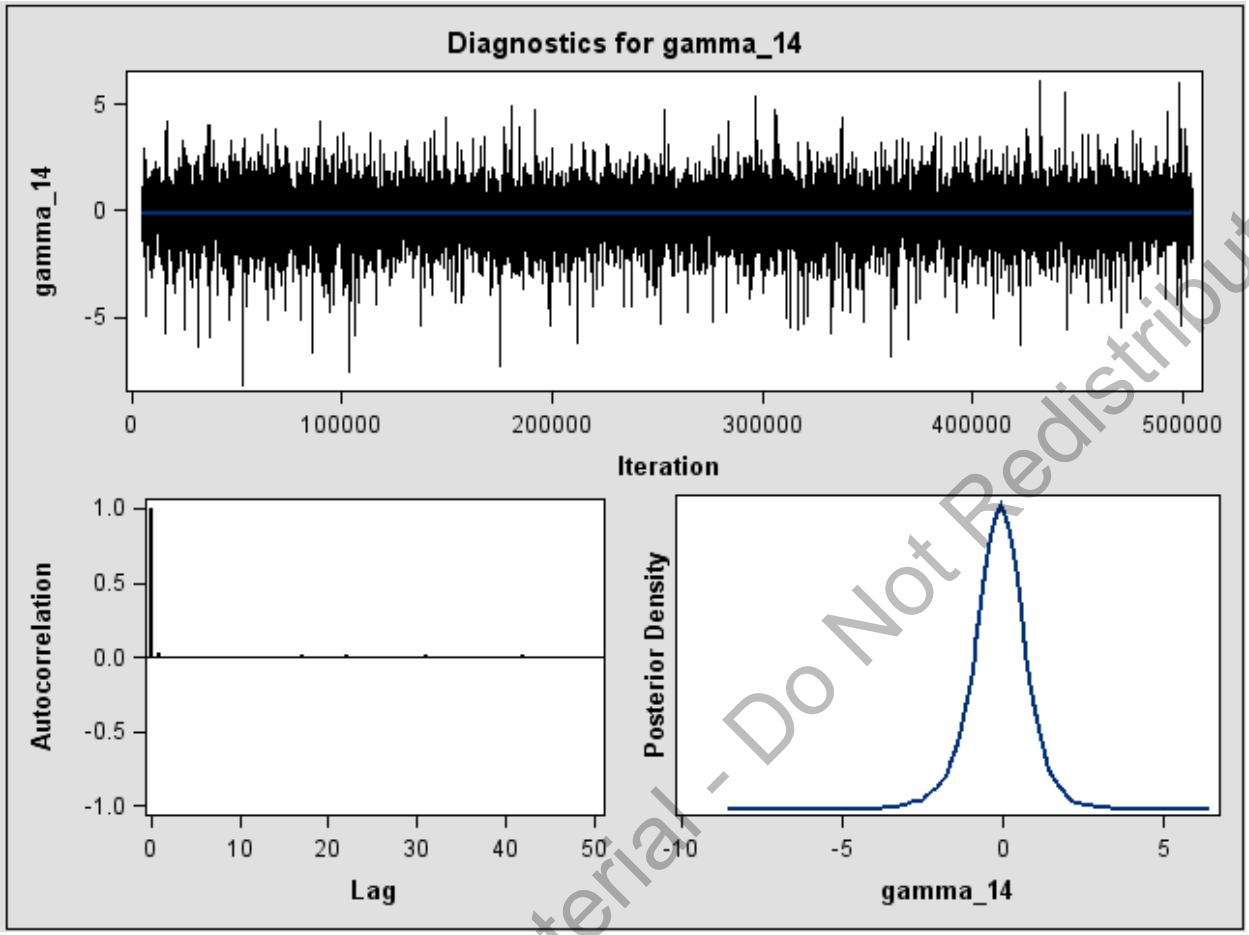
The diagnostic plots for **delta6** show a constant value at 0 (which was expected).



The diagnostic plots for **s2t** (total variance of the likelihood function) show good Markov chain mixing with small autocorrelations after lag 5.



The diagnostic plots for **s2g** (variation of random effects) show excellent Markov chain mixing with small autocorrelations after lag 5.



The random effect parameter for the 14th subject failed the Geweke diagnostic test. The diagnostic plot, however, shows excellent Markov chain mixing. This example shows that the visual inspection of the trace plots is often the most useful approach to assess Markov chain convergence.

Note: The other diagnostic plots (not shown) show similar patterns of convergence.

End of Demonstration

3.2 Meta-Analysis

Objectives

- Define meta-analysis.
- Explain the usefulness of the hierarchical model.
- Illustrate the advantages of meta-analysis.
- Fit a Bayesian model on pooled data sources.

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What Is a Meta-Analysis?

- A *meta-analysis* is a quantitative synthesis of multiple studies that address a set of related research hypotheses.
- The goal is to glean more information from existing data by pooling the results of smaller studies and applying one or more statistical techniques.
- In clinical trials, the treatment effect that might not be detected in small trials might be detected in a meta-analysis that uses data from several trials.

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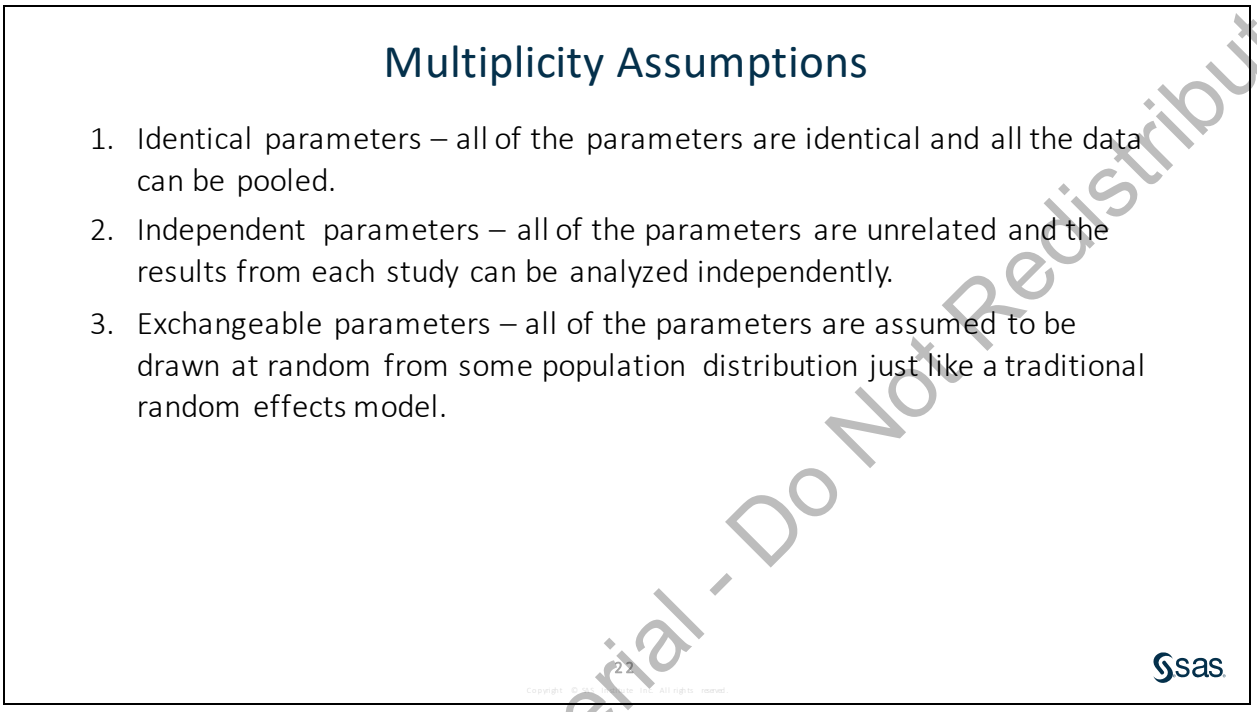
Clinical trials' data are good candidates for meta-analysis as there could be multiple series of trials, analyses of multiple endpoints, multiple subsets of patients, multiple treatment group contrasts, and multiple institutions. The Bayesian approach to meta-analysis gives additional flexibility with the use of nonstandard distributions and the adoption of Markov chain Monte Carlo methods for dealing with complex models.



If you have multiple parameters $\theta_1,...,\theta_k$ corresponding to the treatment effects in situations such as different subsets of patients, multiple institutions, or a series of clinical trials, you can identify three different assumptions regarding the relationships among the parameters. If you assume all of the θ_k are identical and equal to a common treatment effect μ, and if you assume that the observed response Y_k has a normal likelihood, then $Y_k \sim normal(\mu, s_k^2)$, where s_k is the estimated standard errors of θ_k.

If you assume that each θ_k is estimated totally without regard for the others, then the results from each study can be analyzed independently using a fully specified prior distribution within each study.

If you assume that the parameters are exchangeable, then you assume the θ s are drawn at random from some population distribution. This can be considered as a population level distribution for all the studies, but one with unknown parameters. Spiegelhalter et al. (2004) notes that there does not have to be any actual sampling because the assumption of exchangeability is a judgment based on your knowledge of the context. Furthermore, if there are known reasons to suspect that specific studies are systematically different, then those reasons can be modeled by including relevant covariates and then the residual variability more plausibly reflects exchangeability.

Hierarchical Models

The parameters are assumed to be exchangeable and to have a normal distribution

$$\theta_k \sim normal(\mu, \tau^2)$$

where μ and τ^2 are known as hyperparameters.

The unknown hyperparameters can be estimated directly from the data (the empirical Bayes approach) or they can be given a prior distribution (the full hierarchical Bayes approach).

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If the assumption of exchangeability is reasonable, the Bayesian approach is to integrate all the studies into a single model in which it is assumed that $\theta_1,...,\theta_k$ are drawn from some common prior distribution whose parameters are unknown. This is known as the *hierarchical* or *multi-level model*.

These models have inferences for each parameter having narrower credible intervals than if they are assumed independent. They are also shrunk toward the prior mean response. This produces a degree of pooling in which an individual study's results tend to be shrunk by an amount depending on the variability between studies and the precision of the individual study.

The unknown hyperparameters μ and τ^2 can be estimated directly from the marginal likelihood of the data, which avoid the specification of prior distributions for μ and τ^2. On the other hand, μ and τ^2 can be given a prior distribution taking particular care in the choice of the prior distribution for the between-study variation τ^2. Spiegelhalter et al. (2004) points out that the results from either approach will often be similar provided each study is not too small and there are a reasonable number of studies.

The form of the random effects distribution of the θ_k is generally taken to be normal unless evidence shows otherwise. If there is no reason to suspect systematic differences between the studies, a central limit theorem argument can be used to justify normality that arises from the sum of many small unobserved differences between the studies (Spiegelhalter et al. 2004). If the assumption of normality is not reasonable, PROC MCMC enables you to use many other distributions.

The Prior for the Variation between Studies

There might be limited information in the data to provide a precise estimate of τ^2. Three strategies to estimate τ^2 are

1. Elicitation of Opinion – use expert opinion to estimate the upper value of τ^2 .
2. Summary of Evidence – construct a prior distribution from an analysis of past hierarchical models in the context being considered.
3. Default Non-informative Priors – a number of suggestions have been made on the default prior distributions such as inverse gamma and uniform.

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In hierarchical models, the variation of the random effects can be very influential in assessing the uncertainty concerning μ or in predicting future θ s. However, estimating τ^2 can be problematic because either there are too few studies and/or the studies provide little information. This can make the prior for τ^2 very important, and the above slide, using information provided by Spiegelhalter et al. (2004), gives some recommendations on estimating the prior.

When eliciting the opinion of experts, it is important to consider whether there is any variability between θ s. Determining the range of possible values for τ^2 would also be useful.

You can also analyze past hierarchical models in the context being considered to determine reasonable values of τ^2 experienced in practice. For example, you can study the typical variability between subgroups, between institutions in their clinical performance, or between centers in multi-center clinical trials.

With regard to default non-informative priors, Spiegelhalter et al. (2004) recommends the use of a uniform prior on τ^2 as a baseline when there is reasonable information from the data. When prior information is strong or important, a suitably informative prior can be chosen. He concludes that carefully choosing and justifying the prior distributions used within a hierarchical setting is very important in the area of meta-analysis.

Sensitivity Analysis

- *Sensitivity analysis* is the practice of understanding the variation and uncertainty of the posterior inferences as a result of a different prior or likelihood function used in the analysis.
- Given the uncertainty and importance of the hyperparameters, you might want to examine how the conclusions depend on the choice of the prior.
- You can run parallel analyses several times, each time with a different prior, and compare the results.

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An integral part of any meta-analysis is a sensitivity analysis of assumptions concerning the form of the likelihood and the choice of the prior distributions. A sensitivity analysis is supported by the "community of priors" idea introduced by Kass and Greenhouse (1989) that describes the range of viewpoints that should be considered when interpreting evidence.

Recommendations for Sensitivity Analysis

1. Select a suitably flexible class of priors.
2. Examine how the conclusions depend on the choice of the prior.
3. Identify the subsets of priors that would lead to posterior conclusions of specific interest.
4. Report the results and let the audience judge whether their own prior lies in the identified critical subsets of priors.

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Spiegelhalter et. al., (2004) recommend the above steps regarding the implementation of a sensitivity analysis. An example of posterior conclusions of specific interest is the clinical superiority of a treatment.

continued...

Advantages of Meta-Analysis

1. Unified Modeling – hierarchical models can explicitly model between-trial variability.
2. Borrowing Strength – with exchangeable parameters you can borrow strength between the multiple studies and improve the precision for each parameter.
3. Exact Likelihoods – standard normal approximation might not be appropriate when the studies are small.
4. Allowing for Uncertainty in all Parameters – the credible intervals for all parameters are reported.
5. Allowing for Other Sources of Evidence – these sources can be reflected in the prior distributions for parameters.

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Sutton et al. (2000) listed the potential advantages of the Bayesian approach to meta-analysis, which are summarized in the next several slides. Many of these issues can be addressed in a classical perspective, but probably with less flexibility.

continued...

Advantages of Meta-Analysis

6. Allowing Direct Probability Statements on Different Scales – you can make inferences on a variety of scales.
7. Predictions – current meta-analyses can be used in designing future studies.
8. Assessing Compatibility between Meta-Analyses and Individual Clinical Trials – you can assess the compatibility of the likelihood of the new treatment effect with the predictive distribution.
9. Cumulative Meta-Analysis – you can use cumulative meta-analysis as external evidence when monitoring a clinical trial.

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In the area of predictions, you can use the predictive distribution, which takes into account the uncertainty concerning μ and τ^2. Spiegelhalter et al. (2004) points out that this predictive distribution might be a more appropriate summary of the treatment effect compared to conclusions regarding the mean effect μ. The predictive distribution might also be useful for power calculations for confirmatory clinical trials and can also act as a prior distribution in their analysis.

Advantages of Meta-Analysis

10. Meta-Regression – you can investigate the relationship between the treatment effect and study-level factors.
11. Publication Bias – positive studies are more likely to be published, so pooling published and unpublished studies can illustrate the different degrees of publication bias.

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The methods listed in the last three slides are not restricted to randomized clinical trials. The methods might also be applied to meta-analyses of case-control studies and other observational studies with the usual caveats about the adjustment for potential biases (Spiegelhalter et al. 2004).

Example of Meta-Analysis

	Magnesium Group		Control Group		Estimated log-odds ratios
Trial	Deaths	Patients	Deaths	Patients	
1	1	40	2	36	-0.65
2	9	135	23	135	-1.02
3	2	200	7	200	-1.12
4	1	48	1	46	-0.04
5	10	150	8	148	0.21
6	1	59	9	56	-2.05
7	1	25	3	23	-1.03
8	90	1159	118	1157	-0.30
9	2216	29011	2103	29039	0.06

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Example: A series of small randomized clinical trials were conducted to investigate whether intravenous magnesium sulphate has a protective effect after acute myocardial infarction (AMI), particularly through preventing serious arrhythmias. The outcome measure is the estimated log-odds ratios for in-hospital mortality, with values less than 0 favoring magnesium. This measure uses the formula in Spiegelhalter et al. (2004), which adds 0.5 to each cell. The data represent frequency counts of deaths and patients with one active treatment group and one active control group. The results of the clinical trials show a protective effect of intravenous magnesium sulphate for the smaller trials while there was no benefit in the larger clinical trials.

The data are stored in **sasuser.magnesium**. These are the variables in the data set:

trial clinical trial number

rt number of deaths in the magnesium group

nt number of patients in the magnesium group

rc number of deaths in the control group

nc number of patients in the control group

Note: The data were obtained with permission from Spiegelhalter et al. (2004).

Hierarchical Model Using Binomial Likelihood

$$rt_i \sim binomial(nt_i, p_{1i})$$
$$rc_i \sim binomial(nc_i, p_{0i})$$

where *rt* = the number of deaths in magnesium group

nt = the number of patients in the magnesium group

p_1 = the proportion of deaths in the magnesium group

rc = the number of deaths in the control group

nc = the number of patients in the control group

p_0 = the proportion of deaths in the control group

i = clinical trial number

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One approach that combines information from the different clinical trials is to fit a hierarchical model and use the exact binomial likelihood. In this model, the magnesium and control groups have their own binomial likelihood functions to model the number of deaths. The question arises: what should be the prior distribution for the proportion of deaths?

Prior Distributions for Proportion of Deaths

$$p_1[i] \sim beta[a_1, b_1]$$

$$E[p_1] = \frac{a_1}{a_1 + b_1} \qquad \text{var}[p_1] = \frac{a_1}{a_1 + b_1} * \frac{b_1}{a_1 + b_1} * \frac{1}{a_1 + b_1 + 1}$$

If we set $a_1 = \mu_1 * \tau_1$ and $b_1 = (1 - \mu_1) * \tau_1$

then $E[p_1] = \mu_1$ and

$$sd[p_1] = \sqrt{\frac{\mu_1(1 - \mu_1)}{(1 + \tau_1)}}$$

The above hierarchical specification avoids normal approximations of the log-odds ratios.

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The magnesium sulphate meta-analysis example uses the beta distribution for the prior distribution of the proportions of deaths. The above slide shows the mean and variance of the beta distribution. Notice that a beta distribution with hyperparameters $a = \mu\tau$ and $b = (1-\mu)\tau$ has mean μ and a standard deviation $\sqrt{\frac{\mu(1-\mu)}{(1+\tau)}}$. The above hierarchical specification avoids normal approximations of the log-odds ratios, which will be shown in the demonstration.

Bayesian Approach to Meta-Analysis Using Exact Likelihood

Example: Fit a hierarchical model with hyperparameters for the **sasuser.magnesium** data set. Output the posterior samples to a data set. Define two arrays in which one is the proportion of deaths in the treatment group and one is the proportion of deaths in the control group. Use the PARMS statement to define the mean effects of the treatment and control groups with initial values at 0.5, and a scaling factor for the treatment and control groups with initial values of 1. Use another PARMS statement to define the proportion of deaths in the treatment and control groups and set the initial value at 0.5. Then use four PRIOR statements to define the prior distributions for the mean effects (beta(1,1), which is a uniform distribution between 0 and 1), the scaling parameter (gamma(2,iscale of 1), which is a gamma distribution of a mean of 2 and a variance of 2), the proportion of deaths in the treatment group (beta with hyperparameters a1 and b1), and the proportion of deaths in the control group (beta with hyperparameters a0 and b0). Use the BEGINNODATA and ENDNODATA statements to define the hyperparameters and the mean effect difference, the relative risk, the between-study standard deviation of the treatment and control groups, and the log-odds ratio. Finally, use two MODEL statements to model the number of deaths in the treatment group and the number of deaths in the control group (use the binomial distribution).

```
/* stbay03d02.sas */
proc mcmc data=sasuser.magnesium diag=all dic propcov=quanew nbi=5000
     ntu=5000 nmc=650000 plot(smooth)=all thin=15 seed=27513
     mchistory=brief monitor=(diff rel_risk log_or mu1 mu0 s0 s1)
     outpost=meta;
   array p0[9];
   array p1[9];
   parms mu0 0.5 mu1 0.5 tau0 1 tau1 1;
   parms p1: 0.5 p0: 0.5;
   prior mu: ~ beta(1,1);
   prior tau: ~ gamma(2,iscale=1);
   prior p1: ~ beta(a1,b1);
   prior p0: ~ beta(a0,b0);
   beginnodata;
       a1=mu1*tau1;
       b1=(1-mu1)*tau1;
       a0=mu0*tau0;
       b0=(1-mu0)*tau0;
       s0=sqrt(mu0*(1-mu0)/(1+tau0));
       s1=sqrt(mu1*(1-mu1)/(1+tau1));
       diff=mu1-mu0;
       rel_risk=mu1/mu0;
       log_or=log((mu1*(1-mu0))/(mu0*(1-mu1)));
   endnodata;
   model rt ~ binomial(nt,p1[trial]);
   model rc ~ binomial(nc,p0[trial]);
   title "Bayesian Analysis of Meta-Analysis of Magnesium Clinical "
         "Trial Data";
run;
```

The option values in the PROC MCMC statement were selected by a trial and error basis. The model assumes that the death rates (for treatment and control groups) across different studies are distributed independently with a beta distribution with mean mu's and standard deviations s's. The parameters in the two binomial functions include the number of deaths in the treatment and control groups and the proportion of deaths in the treatment and control groups. It should be noted that this approach to meta-analysis assumes that the clinical trials are independent because you are comparing the parameters by summarizing across the clinical trials rather than within clinical trial. If you want to comparisons within trial, then the random effects model would be useful (shown in the next example).

Partial Output

Bayesian Analysis of Meta-Analysis of Magnesium Clinical Trial Data

Number of Observations Read 9
Number of Observations Used 9

Parameters

Block	Parameter	Sampling Method	Initial Value	Prior Distribution
1	mu0	N-Metropolis	0.5000	beta(1,1)
	mu1		0.5000	beta(1,1)
	tau0		1.0000	gamma(2,iscale=1)
	tau1		1.0000	gamma(2,iscale=1)
2	p11	N-Metropolis	0.5000	beta(a1,b1)
	p12		0.5000	beta(a1,b1)
	p13		0.5000	beta(a1,b1)
	p14		0.5000	beta(a1,b1)
	p15		0.5000	beta(a1,b1)
	p16		0.5000	beta(a1,b1)
	p17		0.5000	beta(a1,b1)
	p18		0.5000	beta(a1,b1)
	p19		0.5000	beta(a1,b1)
	p01		0.5000	beta(a0,b0)
	p02		0.5000	beta(a0,b0)
	p03		0.5000	beta(a0,b0)
	p04		0.5000	beta(a0,b0)
	p05		0.5000	beta(a0,b0)
	p06		0.5000	beta(a0,b0)
	p07		0.5000	beta(a0,b0)
	p08		0.5000	beta(a0,b0)
	p09		0.5000	beta(a0,b0)

Tuning History

Phase	RWM Scale Low	RWM Scale High	RWM Acceptance Rate Low	RWM Acceptance Rate High
1	2.380	2.380	0.263	0.591
2	2.380	5.277	0.185	0.268

Burn-In History

RWM Scale Low	RWM Scale High	RWM Acceptance Rate Low	RWM Acceptance Rate High

2.380 5.277 0.186 0.277

Sampling History

RWM Scale		RWM Acceptance Rate	
Low	High	Low	High
2.380	5.277	0.199	0.273

Posterior Summaries

Parameter	N	Mean	Standard Deviation	Percentiles 25	50	75
diff	43334	-0.0374	0.0731	-0.0811	-0.0368	0.00713
rel_risk	43334	0.8559	0.4573	0.5393	0.7530	1.0538
log_or	43334	-0.3252	0.5854	-0.7158	-0.3305	0.0609
mu1	43334	0.1248	0.0494	0.0898	0.1163	0.1499
mu0	43334	0.1622	0.0544	0.1239	0.1547	0.1913
s0	43334	0.1583	0.0434	0.1268	0.1521	0.1829
s1	43334	0.1458	0.0468	0.1120	0.1380	0.1712

Posterior Intervals

Parameter	Alpha	Equal-Tail Interval		HPD Interval	
diff	0.050	-0.1859	0.1084	-0.1830	0.1106
rel_risk	0.050	0.2843	2.0424	0.1833	1.7445
log_or	0.050	-1.4687	0.8467	-1.4849	0.8288
mu1	0.050	0.0547	0.2459	0.0462	0.2257
mu0	0.050	0.0797	0.2907	0.0686	0.2703
s0	0.050	0.0919	0.2604	0.0847	0.2471
s1	0.050	0.0769	0.2584	0.0680	0.2404

The three measures of association (the difference between the mean effects, the relative risk, and the log-odds ratio) show no benefit from magnesium sulphate following myocardial infarction.

Monte Carlo Standard Errors

Parameter	MCSE	Standard Deviation	MCSE/SD
diff	0.000533	0.0731	0.00729
rel_risk	0.00324	0.4573	0.00708
log_or	0.00407	0.5854	0.00695
mu1	0.000396	0.0494	0.00802
mu0	0.000370	0.0544	0.00679
s0	0.000276	0.0434	0.00637
s1	0.000327	0.0468	0.00699

Posterior Autocorrelations

Parameter	Lag 1	Lag 5	Lag 10	Lag 50
diff	0.3179	0.0356	0.0097	-0.0032
rel_risk	0.2798	0.0336	0.0099	0.0039
log_or	0.2719	0.0295	0.0083	-0.0010

mu1	0.3697	0.0502	0.0156	-0.0001
mu0	0.2691	0.0193	0.0061	0.0005
s0	0.2192	0.0129	0.0084	0.0001
s1	0.2925	0.0256	0.0094	0.0009

Geweke Diagnostics

Parameter	z	Pr > |z|
diff	-0.5630	0.5734
rel_risk	-0.0968	0.9229
log_or	-0.2333	0.8155
mu1	-0.3124	0.7547
mu0	0.4458	0.6557
s0	0.4657	0.6414
s1	0.4737	0.6357

Raftery-Lewis Diagnostics

Quantile=0.025 Accuracy=+/-0.005 Probability=0.95 Epsilon=0.001

	Number of Samples			Dependence
Parameter	Burn-In	Total	Minimum	Factor
diff	6	8395	3746	2.2411
rel_risk	5	8366	3746	2.2333
log_or	4	4718	3746	1.2595
mu1	3	4042	3746	1.0790
mu0	3	4088	3746	1.0913
s0	4	4593	3746	1.2261
s1	4	4664	3746	1.2451

Heidelberger-Welch Diagnostics

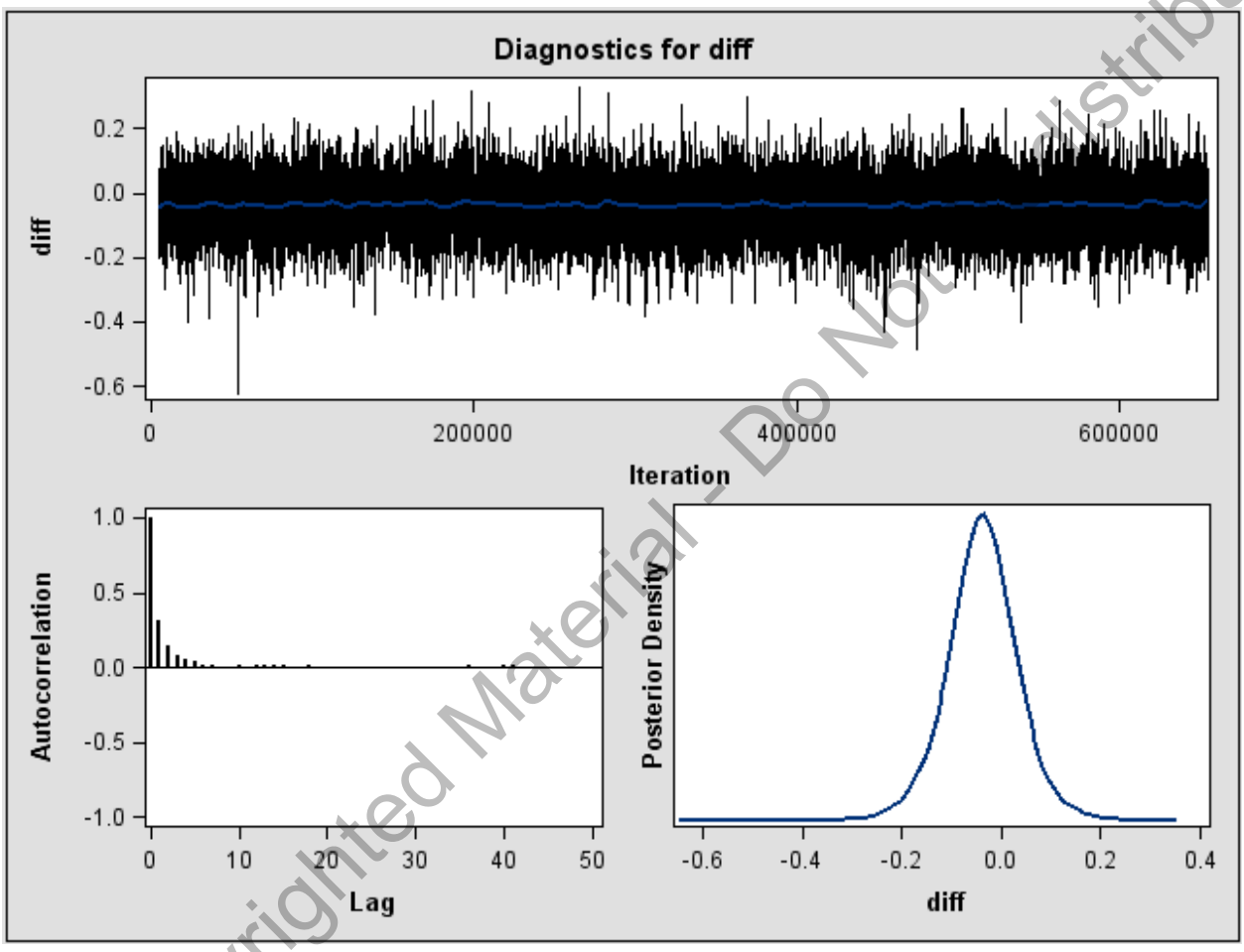
	Stationarity Test			Half-Width Test			
Parameter	Cramer-von Mises Stat	p-Value	Test Outcome	Iterations Discarded	Half-Width	Mean	Relative Half-Width	Test Outcome
diff	0.1027	0.5716	Passed	0	0.00110	-0.0374	-0.0294	Passed
rel_risk	0.1184	0.5019	Passed	0	0.00664	0.8559	0.00776	Passed
log_or	0.0844	0.6666	Passed	0	0.00782	-0.3252	-0.0241	Passed
mu1	0.0495	0.8791	Passed	0	0.000758	0.1248	0.00607	Passed
mu0	0.0986	0.5919	Passed	0	0.000671	0.1622	0.00413	Passed
s0	0.1739	0.3244	Passed	0	0.000537	0.1583	0.00339	Passed
s1	0.0387	0.9397	Passed	0	0.000657	0.1458	0.00451	Passed

Effective Sample Sizes

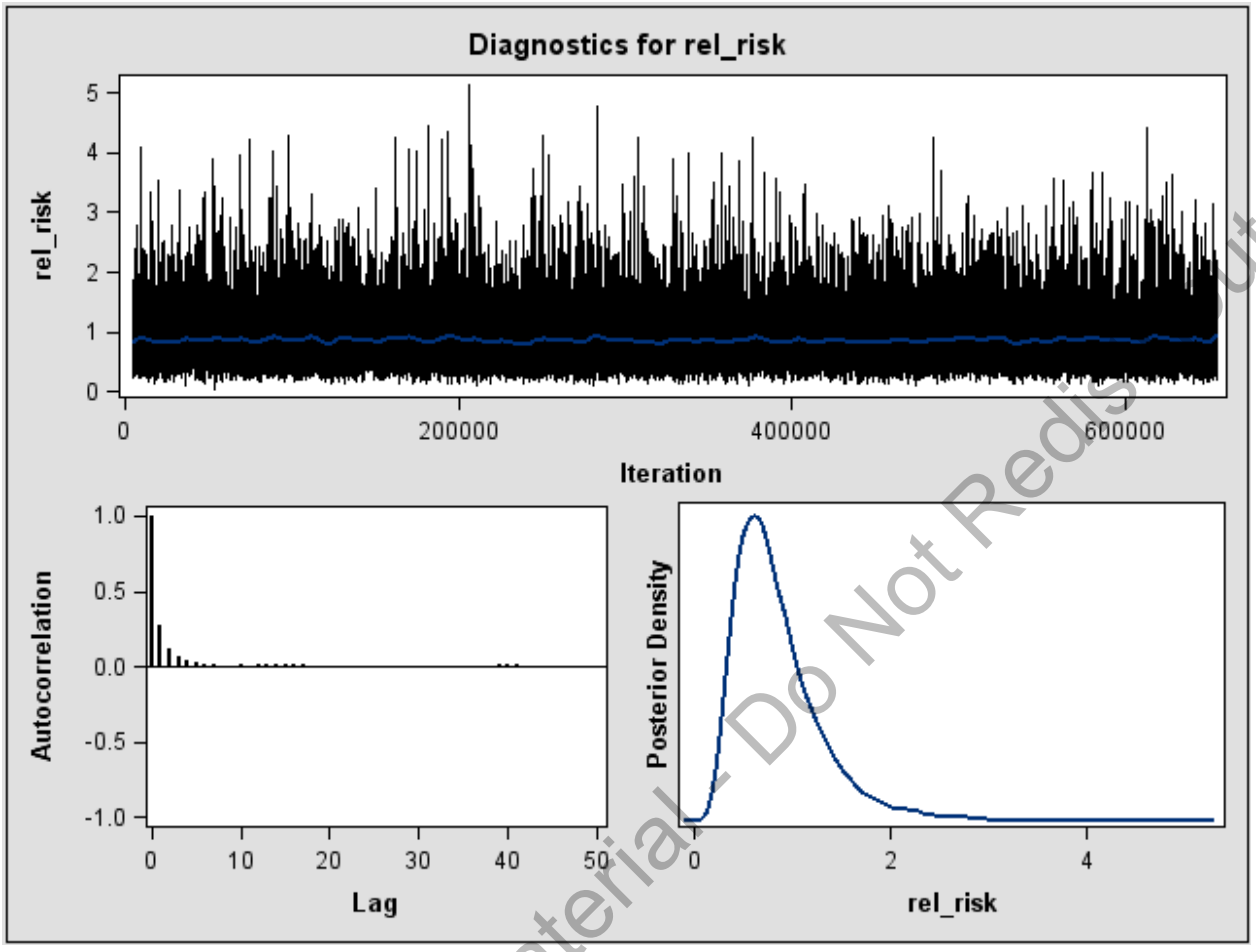
		Autocorrelation	
Parameter	ESS	Time	Efficiency
diff	18803.7	2.3046	0.4339
rel_risk	19939.5	2.1733	0.4601
log_or	20720.1	2.0914	0.4781
mu1	15549.8	2.7868	0.3588
mu0	21674.6	1.9993	0.5002
s0	24671.9	1.7564	0.5693
s1	20439.8	2.1201	0.4717

Deviance Information Criterion	
Dbar (posterior mean of deviance)	90.842
Dmean (deviance evaluated at posterior mean)	74.858
pD (effective number of parameters)	15.984
DIC (smaller is better)	106.826

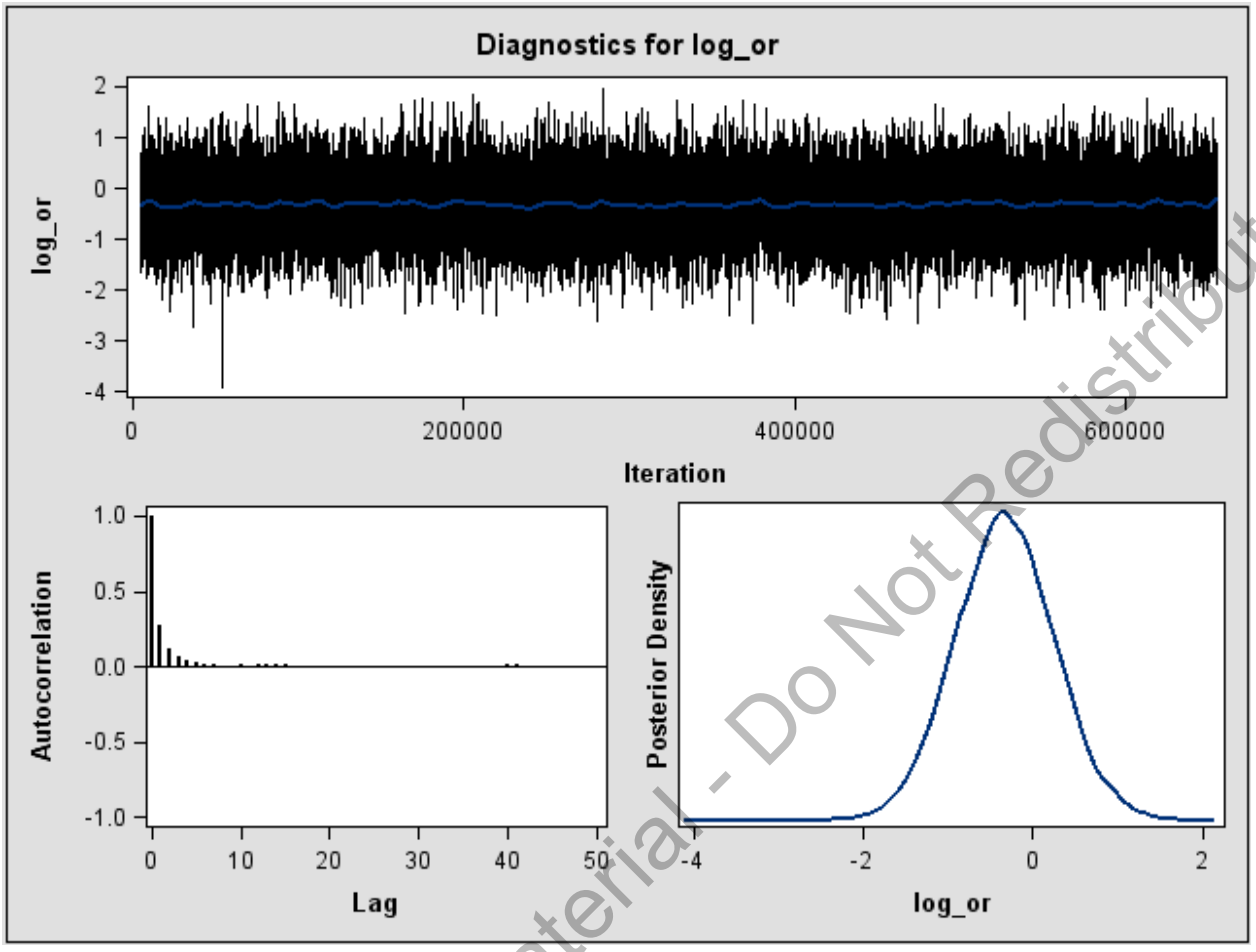
The convergence statistics show no problems with the Markov chain convergence.



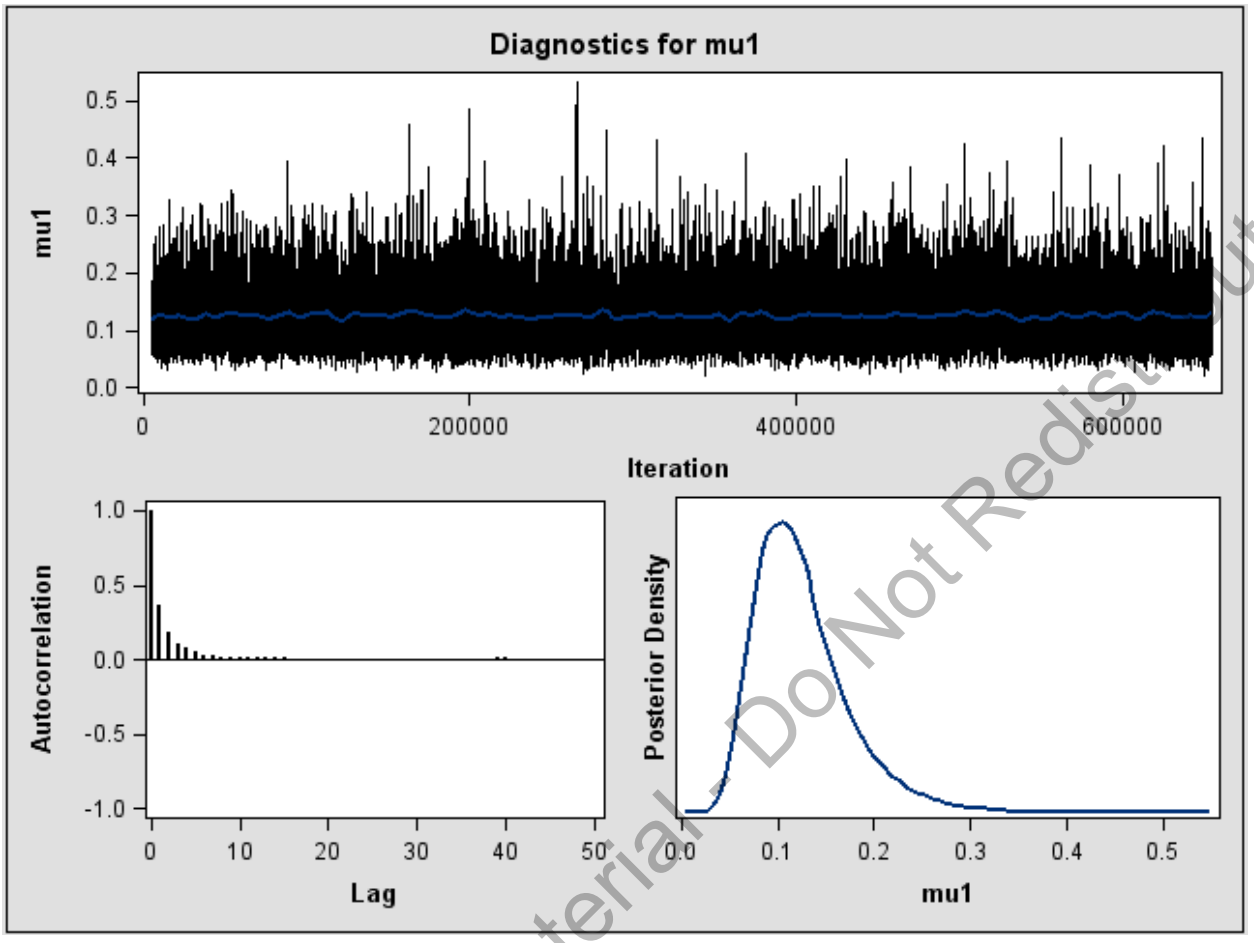
The diagnostics plots for the difference between mean effects show no problems with Markov chain convergence. Notice that 0 is near the center of the posterior density distribution.



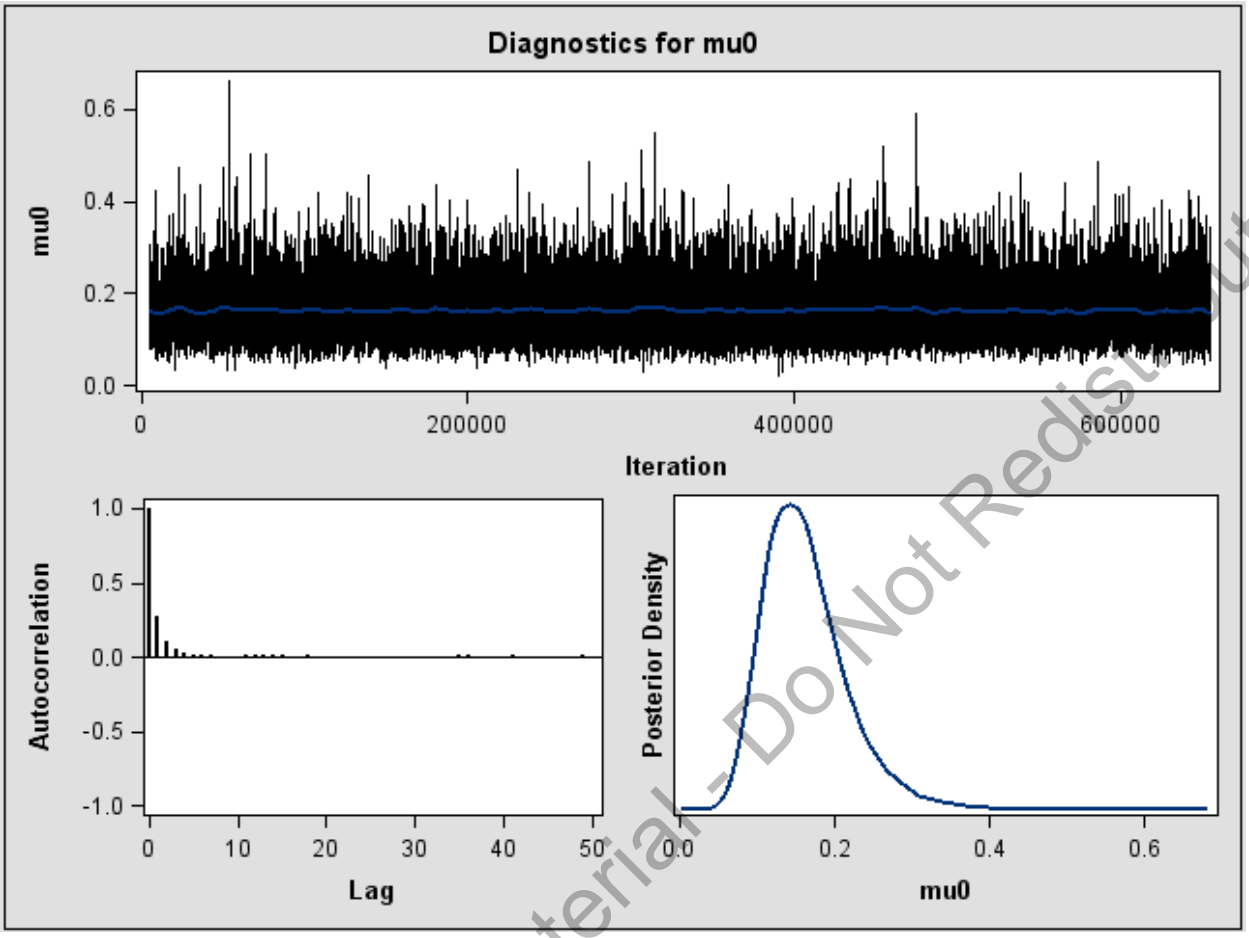
The diagnostic plots for relative risk show no problems with Markov chain convergence. Notice that 1 is near the center of the mass of the posterior density distribution.



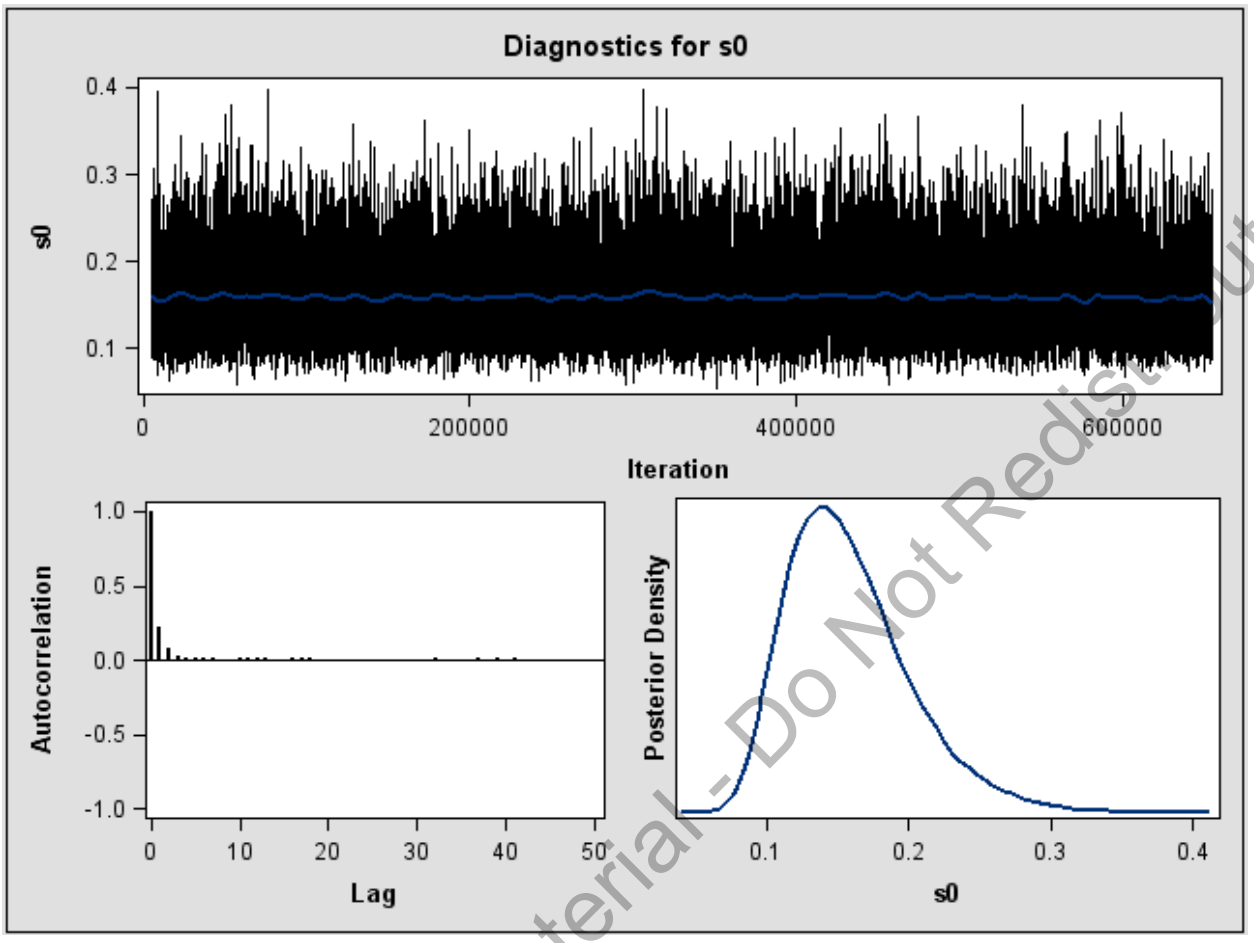
The diagnostic plots for the log-odds ratio show no problems with the Markov chain convergence. Notice that 0 is near the center of the posterior density distribution.



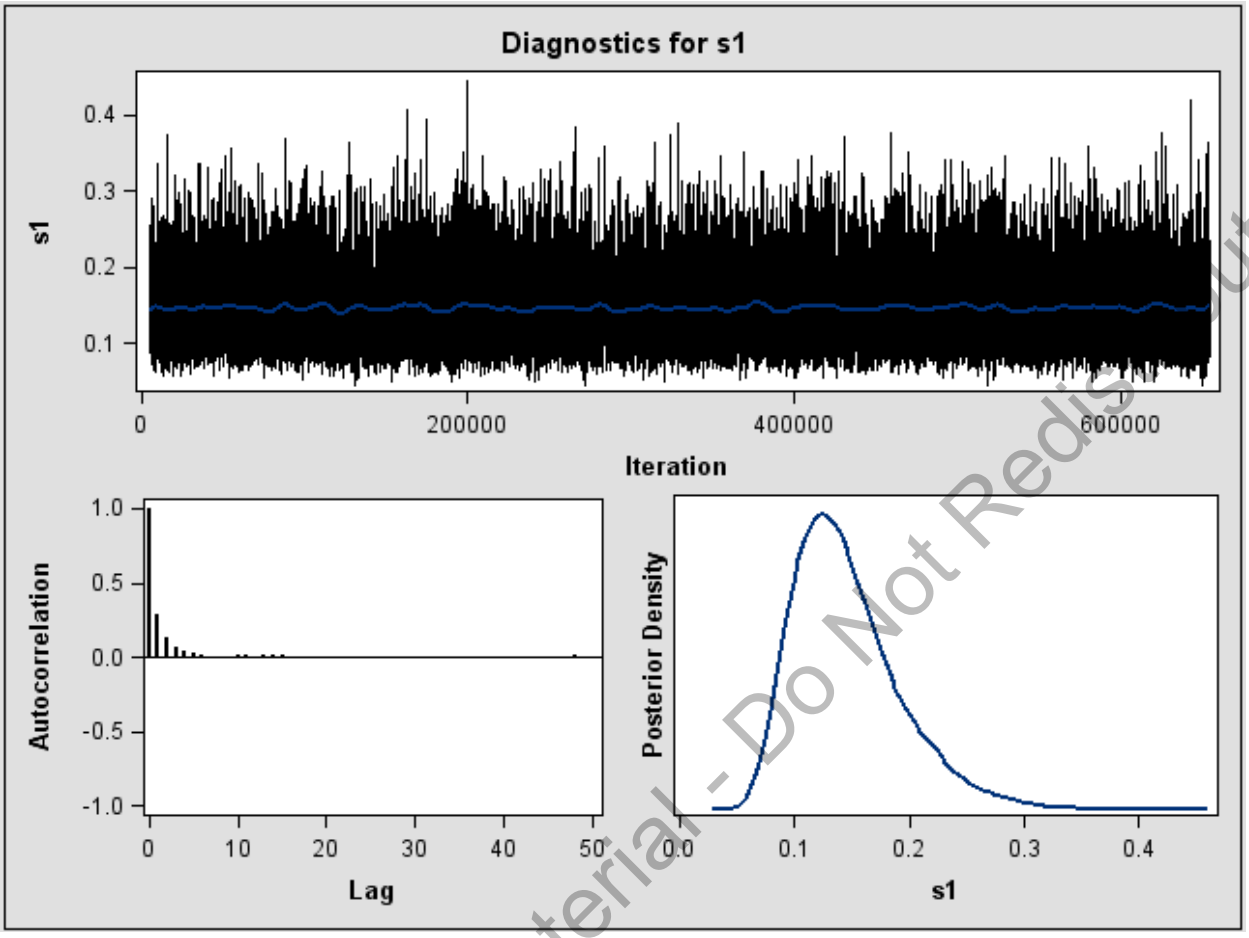
The diagnostic plots for the mean effect in the treatment group show no problems with Markov chain convergence.



The diagnostic plots for the mean effect in the control group show no problems with Markov chain convergence.



The diagnostic plots for the between-trial standard deviation in the control group show no problems with Markov chain convergence.



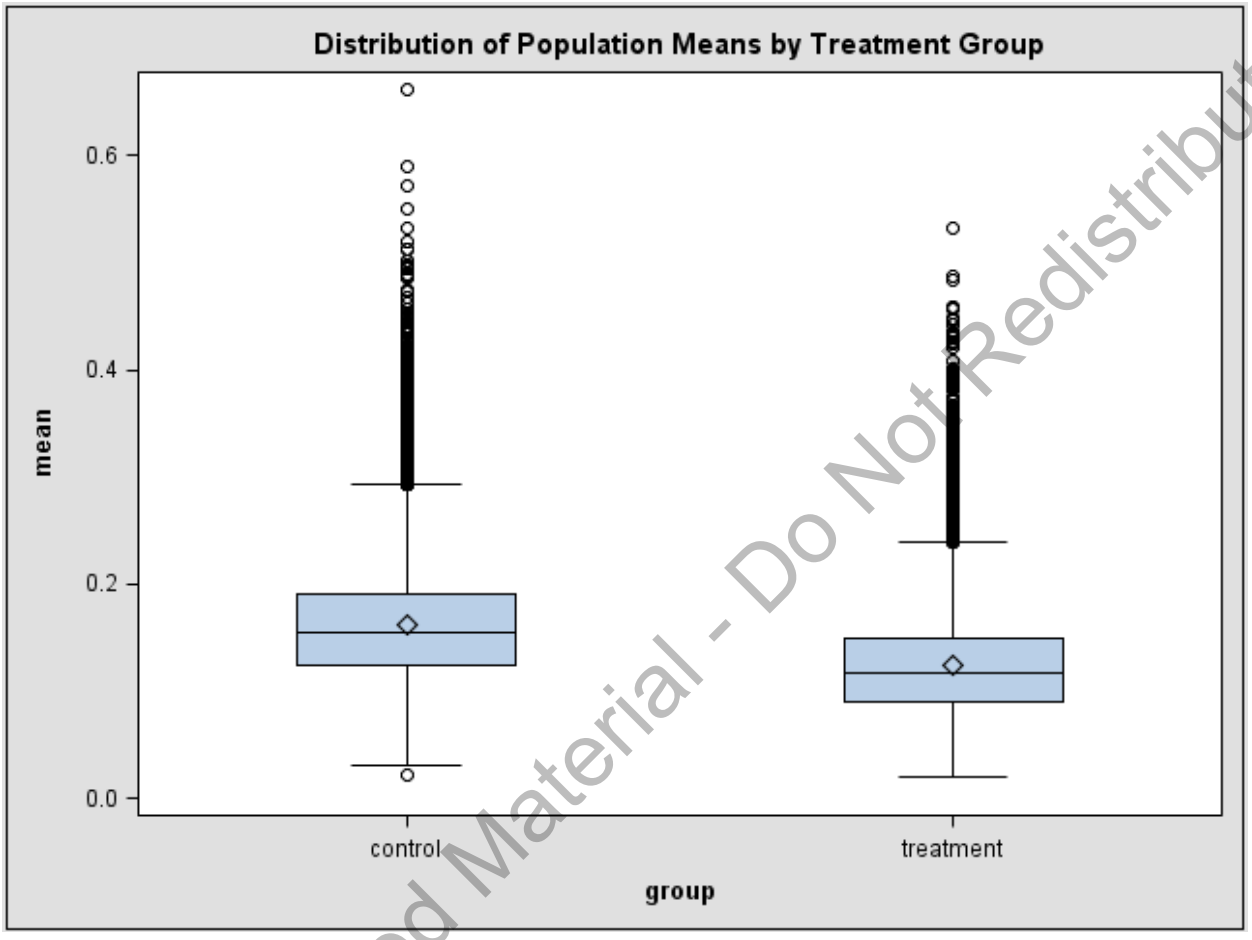
The diagnostic plots for the between-trial standard deviation in the treatment group show no problems with Markov chain convergence.

Example: Create a box plot comparing the means for the treatment group and the means for the control group.

```
data mean_treatment (keep=mu1) mean_control (keep=mu0);
   set meta;
run;

data boxplot;
   set mean_treatment (in=treat) mean_control (in=control);
   if treat then do;
      mean=mu1;
      group='treatment';
   end;
   if control then do;
      mean=mu0;
      group='control';
   end;
run;
```

```
proc sgplot data=boxplot;
   vbox mean / category=group;
   title "Distribution of Population Means by Treatment Group";
run;
```



The box plot shows no apparent differences between the mean effects in the treatment group and the mean effects in the control group.

End of Demonstration

Hierarchical Model Using Normal Approximation

$$OR_i = \frac{rt_i * (nc_i - rc_i)}{rc_i * (nt_i - rt_i)}$$

You can estimate the treatment effect through the means of an approximate normal distribution,

$$\log(OR_i) \sim normal(\theta_i, s_i^2)$$

Because the clinical trials have relatively large sample sizes, you can use the approximate sampling variance:

$$s_i^2 = \frac{1}{rt_i} + \frac{1}{nt_i - rt_i} + \frac{1}{rc_i} + \frac{1}{nc_1 - rc_i}$$

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The normal approximation to the binomial likelihood is a classical method that is commonly used in meta-analysis. However, the approximation becomes less precise in the extreme probabilities (close to 0 or 1). In that situation, the exact likelihood approach should be used. If the clinical trials have relatively large sample sizes, the approximate sampling variance can be used.

Hierarchical Model Using Normal Approximation

If the odds ratios are exchangeable between the clinical trials, then you can place a common prior distribution of the parameters θ_i ,

$$\theta_i \sim normal(\mu, \tau^2)$$

Noninformative priors are placed on the hyperparameters:

$$\mu \sim normal(0, sd = 10)$$

$$\tau^2 \sim igamma(shape = 2.001, scale = 1.001)$$

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The treatment effect of each trial, θ_i, will be treated as a random effect. This will allow us to identify studies that are very different from the others. The hyperparameter μ is the population average of the treatment effect across all clinical trials and τ^2 is the between-study variation.

Bayesian Approach to Meta-Analysis Using Normal Approximation

Example: Compute the log of the odds ratio and its approximate sampling variance. Then fit a hierarchical model with hyperparameters and output the posterior samples to a data set. Use the ARRAY statement to define an array for the odds ratios across the clinical trials and use the PARMS statement to define the hyperparameters for the population average and between-study variation. Also use the PRIOR statement to specify noninformative priors and use the RANDOM statement to define the random effect **theta** with a normal prior distribution with the mean and variance defined by the hyperparameters. Allocate an array and store the transformation of the random effects in the array. Then compute the pooled treatment effect by exponentiating the hyperparameter for the population average. Use the MODEL statement to specify the normal likelihood for the log odds ratios and use the %CATER autocall macro to create a caterpillar plot of the odds ratios.

```
/*  stbay03d03.sas  */
data magnesiumalt;
     set sasuser.magnesium;
     logy=log((rt*(nc-rc))/(rc*(nt-rt)));
     sigma2=1/rt + 1/(nt-rt) + 1/rc + 1/(nc-rc);
run;

proc mcmc data=magnesiumalt diag=all dic nbi=10000 stats=all
     ntu=5000 nmc=200000 plot(smooth)=all seed=27513 mchistory=brief
     monitor=(mu tau2 OR Pooled) outpost=metapooled;
       array OR[9];
       parms mu 0.5 tau2 1;
       prior mu ~ normal(0, sd=10);
       prior tau2 ~ igamma(2.001,s=1.001);
       random theta ~ normal(mu, var=tau2) subject=trial;
       OR[trial]=exp(theta);
       Pooled=exp(mu);
       model logy ~ normal(theta, var=sigma2);
run;
```

The option values in the PROC MCMC statement were selected by a trial and error basis. The MONITOR= option outputs analysis for the two hyperparameters, the odds ratios, and the pooled treatment effect. The ARRAY statement allocates an array variable OR of size 9, which is the number of clinical trials. The RANDOM statement declares **theta** as a random effect and specifies the normal prior distribution with hyperparameters **mu** and **tau2**. The SUBJECT=option specifies the group index using the variable **trial**. The RANDOM statement will generate 9 random effect parameters, one for each clinical trial. The OR array stores the exponentiation of the random effect parameters indexed by the clinical trial number (this would only work if **trial** consisted of integer values). The symbol **Pooled** calculates the exponential of the hyperparameter **mu**, which is the pooled treatment effect. The MODEL statement specifies that the response variable **logy** (the log of the odds ratios) has a normal distribution with a mean of **theta** (the study-specific effect) and a variance of **sigma2** (the approximate sampling variance).

Partial Output

Bayesian Analysis of Meta-Analysis of Magnesium Clinical Trial Data
Using Random Effects and Normal Approximation to the Likelihood

Number of Observations Read 9
Number of Observations Used 9

Parameters

Block	Parameter	Sampling Method	Initial Value	Prior Distribution
1	mu	Conjugate	0.5000	normal(0, sd=10)
2	tau2	Conjugate	1.0000	igamma(2.001,s=1.001)

Random Effect Parameters

Parameter	Sampling Method	Subject	Number of Subjects	Subject Values	Prior Distribution
theta	Conjugate	trial	9	1 2 3 4 5 6 7 8 9	normal(mu, var=tau2)

Posterior Summaries

Parameter	N	Mean	Standard Deviation	Percentiles 25	50	75
mu	200000	-0.5393	0.3258	-0.7427	-0.5274	-0.3221
tau2	200000	0.5091	0.3324	0.2967	0.4222	0.6179
OR1	200000	0.6756	0.4985	0.3636	0.5570	0.8412
OR2	200000	0.4356	0.1633	0.3192	0.4089	0.5220
OR3	200000	0.5068	0.2964	0.3033	0.4432	0.6359
OR4	200000	0.8059	0.6697	0.4173	0.6430	0.9878
OR5	200000	1.0376	0.4507	0.7233	0.9495	1.2515
OR6	200000	0.4228	0.2835	0.2284	0.3579	0.5426
OR7	200000	0.5996	0.4231	0.3250	0.4997	0.7535
OR8	200000	0.7409	0.1068	0.6659	0.7333	0.8076
OR9	200000	1.0583	0.0335	1.0354	1.0577	1.0806
Pooled	200000	0.6143	0.2011	0.4758	0.5901	0.7246

Posterior Intervals

Parameter	Alpha	Equal-Tail Interval		HPD Interval	
mu	0.050	-1.2160	0.0715	-1.1890	0.0964
tau2	0.050	0.1632	1.3709	0.1132	1.1322
OR1	0.050	0.1459	1.9088	0.0611	1.5606
OR2	0.050	0.1967	0.8269	0.1647	0.7621
OR3	0.050	0.1370	1.2548	0.0822	1.0788
OR4	0.050	0.1675	2.4110	0.0690	1.9217
OR5	0.050	0.4314	2.1553	0.3394	1.9256
OR6	0.050	0.0840	1.1448	0.0355	0.9599
OR7	0.050	0.1279	1.6615	0.0583	1.3772
OR8	0.050	0.5533	0.9711	0.5418	0.9559
OR9	0.050	0.9942	1.1256	0.9937	1.1251
Pooled	0.050	0.2964	1.0742	0.2587	1.0088

Odds ratios below 1 indicate a protective effect of intravenous magnesium sulphate. Although the pooled odds ratio is below 1, both credible intervals go across 1.

Monte Carlo Standard Errors

Parameter	MCSE	Standard Deviation	MCSE/SD
mu	0.00126	0.3258	0.00386
tau2	0.00120	0.3324	0.00360
OR1	0.00132	0.4985	0.00265
OR2	0.000430	0.1633	0.00263
OR3	0.000822	0.2964	0.00277
OR4	0.00176	0.6697	0.00262
OR5	0.00114	0.4507	0.00254
OR6	0.000843	0.2835	0.00298
OR7	0.00114	0.4231	0.00269
OR8	0.000243	0.1068	0.00228
OR9	0.000075	0.0335	0.00224
Pooled	0.000757	0.2011	0.00376

Posterior Autocorrelations

Parameter	Lag 1	Lag 5	Lag 10	Lag 50
mu	0.4674	0.0414	0.0037	0.0028
tau2	0.4049	0.0276	-0.0031	-0.0013
OR1	0.1011	0.0092	0.0002	0.0030
OR2	0.0904	0.0094	0.0051	-0.0014
OR3	0.1203	0.0126	0.0051	-0.0005
OR4	0.1111	0.0053	0.0009	0.0008
OR5	0.0891	0.0035	0.0036	-0.0041
OR6	0.1763	0.0170	0.0025	0.0010
OR7	0.1112	0.0128	-0.0011	0.0039
OR8	0.0117	-0.0004	-0.0013	0.0010
OR9	0.0001	-0.0017	0.0019	-0.0005
Pooled	0.4468	0.0375	0.0011	0.0023

Geweke Diagnostics

Parameter	z	Pr > |z|
mu	0.7427	0.4576
tau2	-0.8956	0.3704
OR1	0.3383	0.7352
OR2	0.7987	0.4245
OR3	0.1083	0.9138
OR4	-1.1301	0.2584
OR5	0.1833	0.8546
OR6	0.5924	0.5536
OR7	1.7134	0.0866
OR8	0.6879	0.4915
OR9	-0.6138	0.5393
Pooled	0.6426	0.5205

Raftery-Lewis Diagnostics

Quantile=0.025 Accuracy=+/-0.005 Probability=0.95 Epsilon=0.001

Parameter	Number of Samples Burn-In	Total	Minimum	Dependence Factor
mu	5	8583	3746	2.2912
tau2	4	7869	3746	2.1006
OR1	4	7883	3746	2.1044
OR2	2	3894	3746	1.0395
OR3	4	7829	3746	2.0900
OR4	4	7904	3746	2.1100
OR5	2	3870	3746	1.0331
OR6	5	8214	3746	2.1927
OR7	4	7686	3746	2.0518
OR8	2	3794	3746	1.0128
OR9	2	3710	3746	0.9904
Pooled	5	8583	3746	2.2912

Heidelberger-Welch Diagnostics

Parameter	Stationarity Test Cramer-von Mises Stat	p-Value	Test Outcome	Iterations Discarded	Half-Width Test Half-Width	Mean	Relative Half-Width	Test Outcome
mu	0.2741	0.1603	Passed	0	0.00216	-0.5393	-0.00401	Passed
tau2	0.1205	0.4935	Passed	80000	0.00257	0.5111	0.00504	Passed
OR1	0.0529	0.8582	Passed	0	0.00228	0.6756	0.00337	Passed
OR2	0.1265	0.4698	Passed	0	0.000901	0.4356	0.00207	Passed
OR3	0.1175	0.5055	Passed	0	0.00161	0.5068	0.00317	Passed
OR4	0.0926	0.6226	Passed	0	0.00395	0.8059	0.00490	Passed
OR5	0.0972	0.5990	Passed	0	0.00233	1.0376	0.00225	Passed
OR6	0.3686	0.0876	Passed	0	0.00148	0.4228	0.00350	Passed
OR7	0.3276	0.1132	Passed	0	0.00216	0.5996	0.00360	Passed
OR8	0.1076	0.5491	Passed	0	0.000424	0.7409	0.000573	Passed
OR9	0.1143	0.5193	Passed	0	0.000131	1.0583	0.000124	Passed
Pooled	0.1935	0.2804	Passed	0	0.00131	0.6143	0.00214	Passed

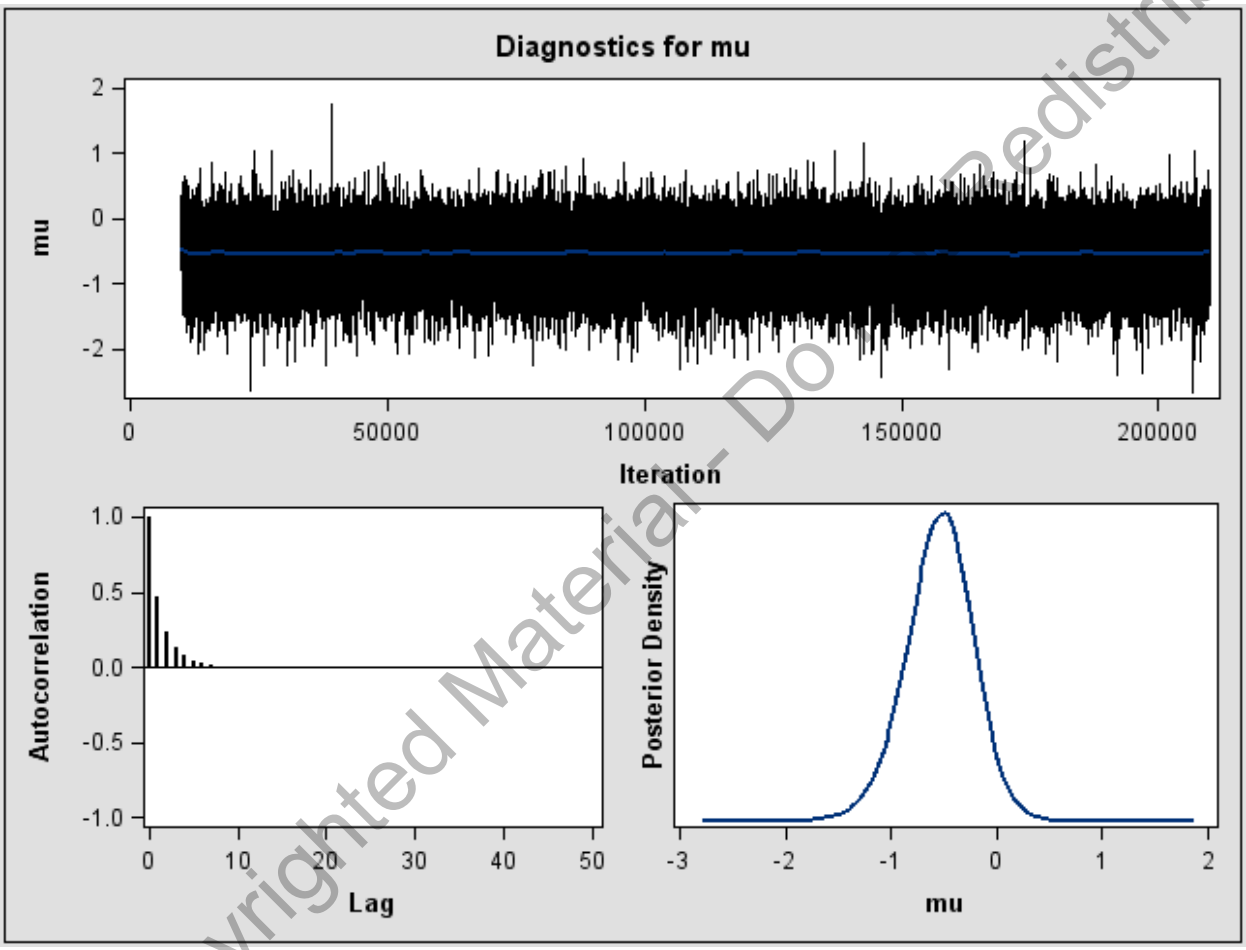
Effective Sample Sizes

Parameter	ESS	Autocorrelation Time	Efficiency
mu	67077.9	2.9816	0.3354
tau2	77084.5	2.5946	0.3854
OR1	141978.5	1.4087	0.7099
OR2	144347.5	1.3855	0.7217
OR3	130057.1	1.5378	0.6503
OR4	145442.0	1.3751	0.7272
OR5	155414.5	1.2869	0.7771
OR6	112969.5	1.7704	0.5648
OR7	138386.7	1.4452	0.6919
OR8	192816.7	1.0373	0.9641
OR9	200000.0	1.0000	1.0000
Pooled	70558.3	2.8345	0.3528

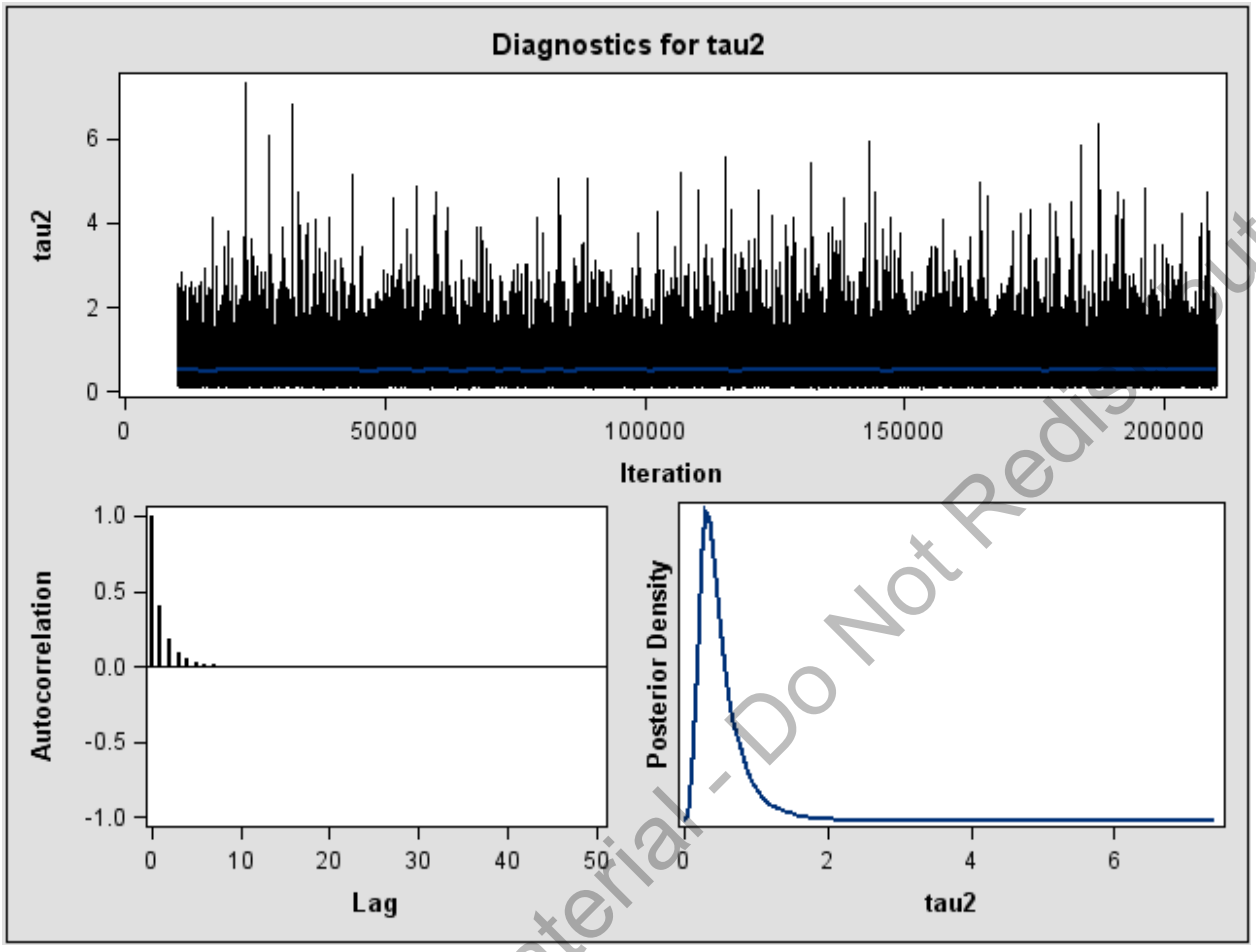
Deviance Information Criterion	
Dbar (posterior mean of deviance)	11.583
Dmean (deviance evaluated at posterior mean)	6.493
pD (effective number of parameters)	5.090
DIC (smaller is better)	16.672

The convergence statistics show no problems with the Markov chain convergence.

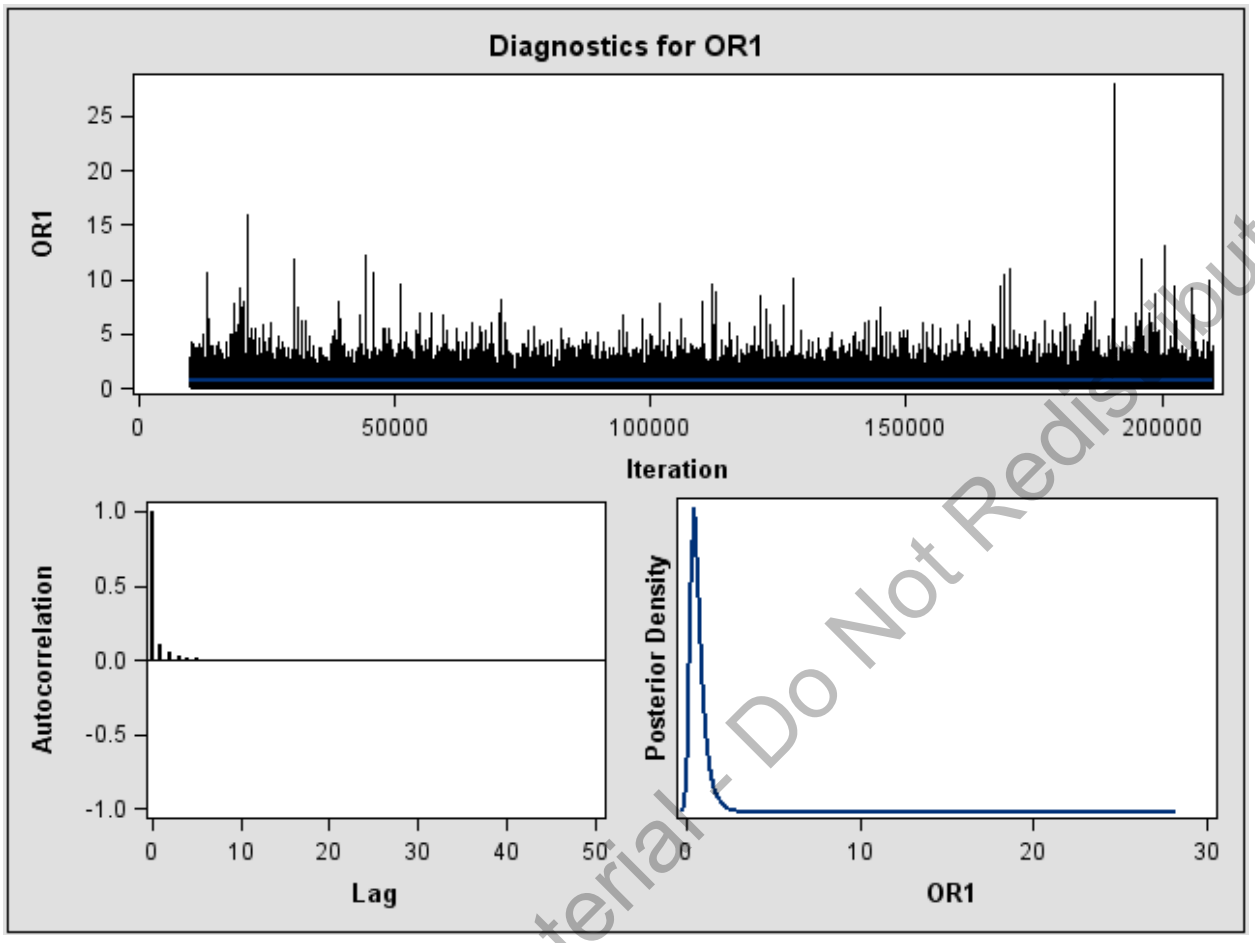
Partial Graphics Output



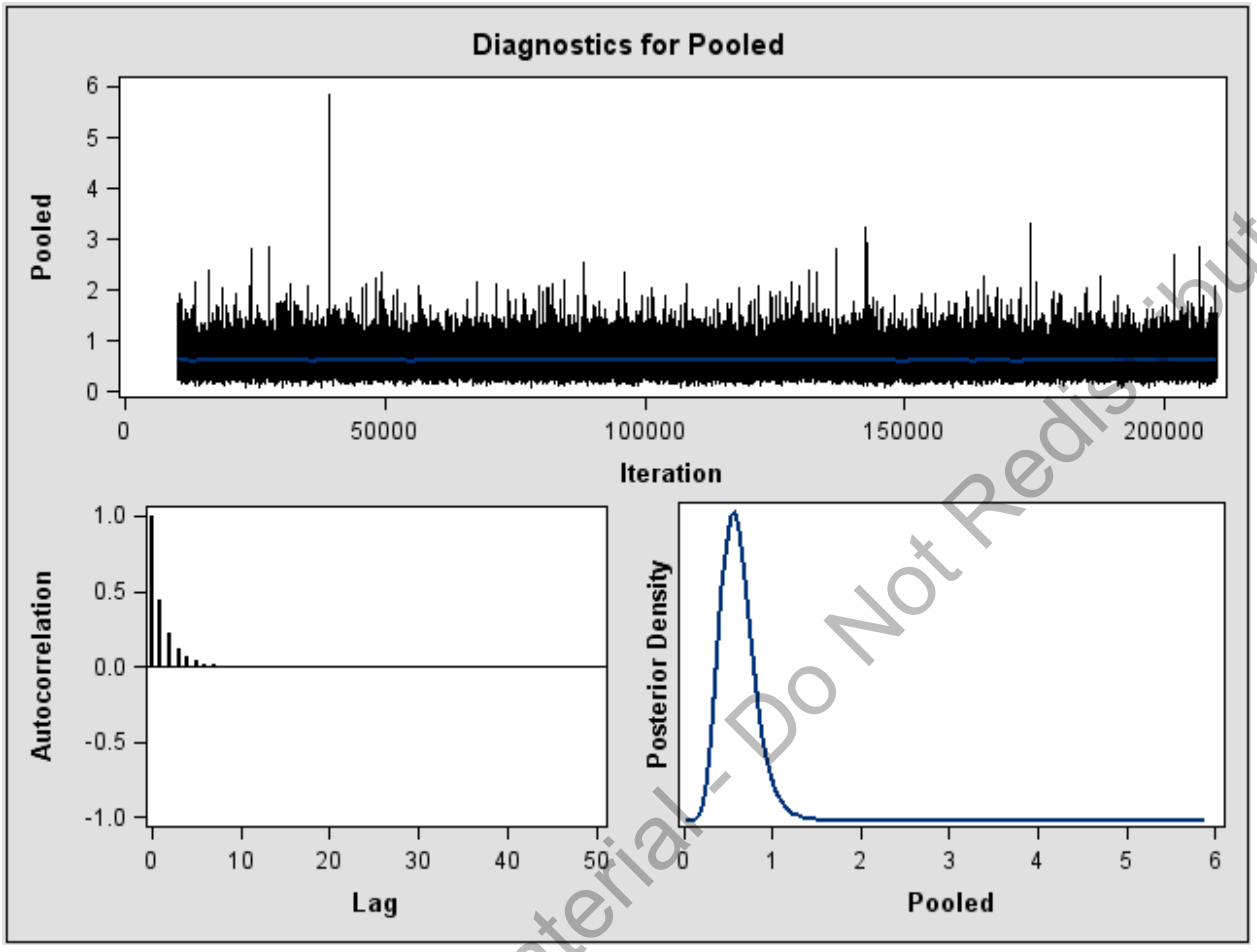
The diagnostic plots for **mu**, the population average of the treatment effect across all the studies, show no problems with Markov chain convergence.



The diagnostic plots for **tau2**, the between-study variation, show no problems with Markov chain convergence.



The diagnostic plots for the odds ratio for clinical trial 1 show no problems with Markov chain convergence.

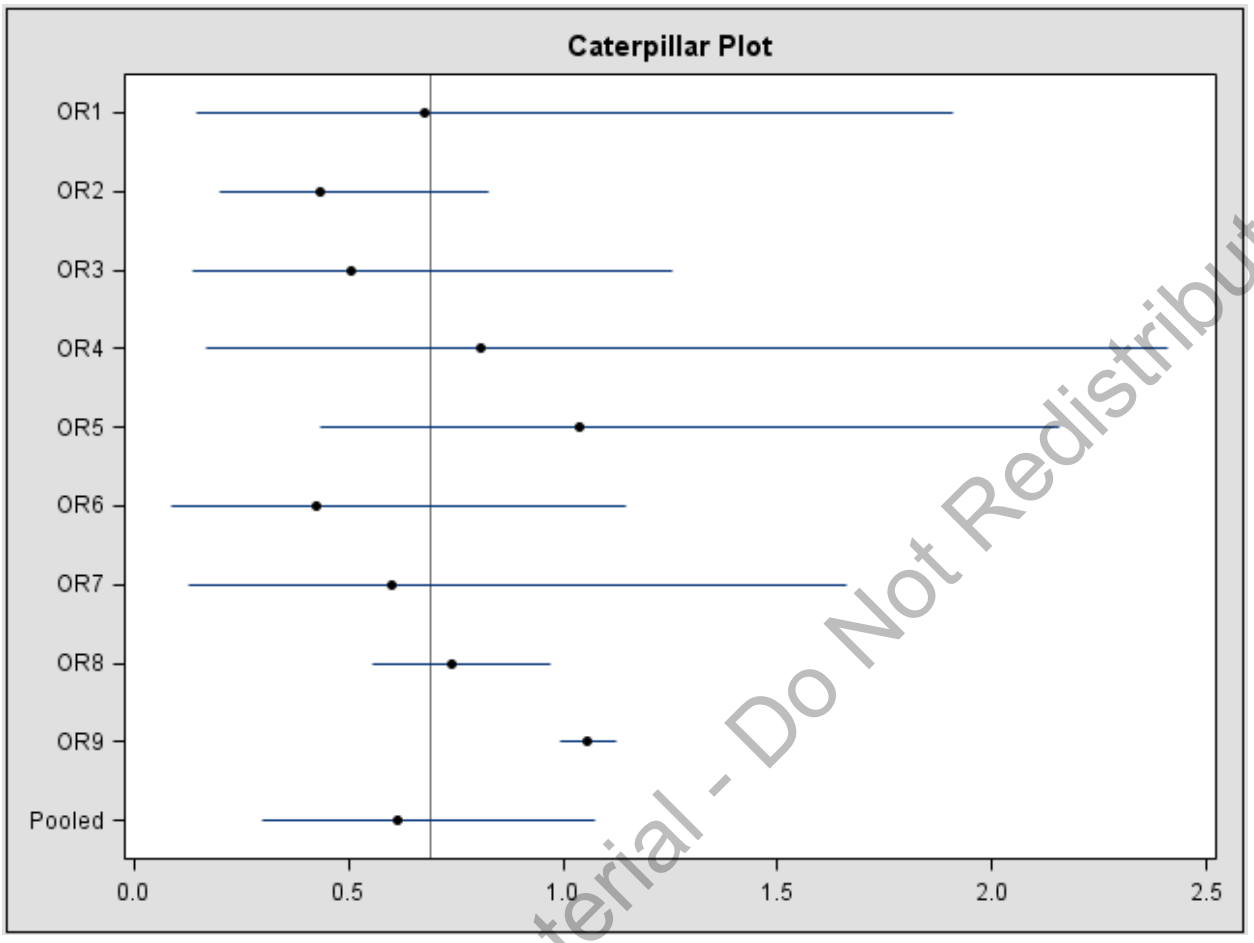


The diagnostic plots for the pooled odds ratio across the clinical trials show no problems with Markov chain convergence.

Note: The other diagnostic plots (not shown) show similar patterns of convergence.

```
%CATER(data=metapooled, var=OR: Pooled);
```

The CATER macro takes the output data set that contains the posterior samples of all the model parameters and generates a caterpillar plot of all clinical trial-specific odds ratios and the pooled odds ratio.



The reference line is at the overall mean (in this case 0.70). The intervals are the 95% equal-tail credible intervals. Notice that most of the credible intervals go across 1. The graph illustrates the advantage of the random-effects model. In the first meta-analysis model, the parameters that were computed compared the treatment group to the control group across the clinical trials. In the second meta-analysis model, parameters were computed for each clinical trial and you can identify clinical trials that are very different from the others, such as ones with very high or very low treatment effects.

Note: If you want to change the display of the caterpillar plot, such as using a different line pattern, color, or size of the markers, you need to first modify the **Stat.MCMC.Graphics.Caterpillar** template and then call the %CATER macro again.

End of Demonstration