Assessment of the scientific documentation of the drugs etidronat (Didronate) and alendronat (Fosamax) for the reduction of the number of fractures among women with osteoporosis.
An analysis based on Bayesian statistics.

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Chapter 1

Introduction and conclusion

This report contains an analysis of the scientific documentation of the effect of the drugs etidronat (Didronate) and alendronat (Fosamax) in reducing the number of fractures in women with osteoporosis. The background for the analysis are data from existing studies (Storm et al. (1990), Harris et al. (1993), Liberman et al. (1995) and Black et al. (1996)).

As criterion for evaluation, we have used a comparison of the relative improvement in effect for the two drugs compared to a placebo. On a slightly smaller scale, a cost assessment of the drugs was performed; this analysis is, however, based on more assumptions and is thus more speculative. The validity of the results must be viewed in light of these assumptions. Due to time restrictions we have only looked at improvement in effect over a 3 year period.

From a statistical point of view the analysis stands out from other studies in three areas:

1. The methodological foundation is based on Bayesian statistics. This makes it possible to evaluate and take into account the uncertainty that lies within improvement in effect in a simpler and more consistent way.

2. Data from different studies are combined to give a more reliable assessment of the drugs. The combination of data is also accomplished with the aid of Bayesian statistics.

3. A cost analysis of the two drugs has been undertaken - again based on Bayesian statistics.

A complicating factor regarding the studies that are available, is that the prevalence of osteoporosis in the populations that have been tested varies to a large degree. It is nonetheless possible to combine the studies if it is assumed that the *relative improvement in effect* of the drug is the same for all levels of prevalence. An alternative is to analyse only those studies (Harris et al. (1993) and Black et al. (1996)) where the prevalence of osteoporosis is similar. We look at both of these possibilities.

Another complicating factor involves the differences in specificity among the different studies. If one accepts a vertebral fracture as an indication of osteoporosis, one achieves, as in the investigation of Black et al. (1996), a higher diagnostic specificity by excluding fractures where adequate trauma existed. Correcting for this causes the difference in effectiveness between etidronat and alendronat to be somewhat smaller than described below. Furthermore, differences in specificity will naturally become apparent such that investigations conducted on populations with a high prevalence of osteoporosis tend to yield higher relative effect of medicinal intervention compared to populations with lower prevalence. Presumably there were few vertebral fractures with adequate trauma, such that the effect of overlooking them was small. A reasonable assessment of this has not, to-date, been possible with the available data.

In conclusion, we have clearly documented that both drugs are effective in reducing the number of vertebral fractures in women with osteoporosis; alendronat (Fosamax) being the better of the two.

To assess the costs in using these drugs for reducing the number of hip fractures, we have assumed that the relative reduction in the intensity of hip fracture is the same as the relative reduction in intensity of vertebral fracture. Data from the study of Black et al. (1996) give a basis for this assumption with respect to alendronat. Table 2 in that study showed a relative risk of 0.45 (CI $[0.27, 0.72]$) for vertebral fracture, while Table 3 showed a relative risk of 0.49 (CI $[0.23, 0.99]$) for hip fracture and a relative risk of 0.52 (CI $[0.31, 0.87]$) for wrist fracture. All of these effects are statistically significant at the 0.05 level. Data from etidronat studies give the impression that the same assumption also is true for this drug; however there is a larger degree of uncertainty due to the size of the data material.

With respect to the reduction in the number of hip fractures in women with osteoporosis, our cost assessment of the two drugs indicates that alendronat (Fosamax) can be priced 40 - 70 % higher than etidronat (Didronate).

Other types of fractures have not been evaluated. The study of Black et al. (1996) gives a basis for assuming that the relative improvement in the reduction of wrist fractures is also comparable to the relative improvement in the reduction of the number of vertebral fractures.

Chapter 2 includes an analysis of the two drugs compared to a placebo. A separate comparison between the two drugs was also performed. Chapter 3 includes a simple cost analysis of the drugs. The methodological and technical details are outlined in Appendix A.

Chapter 2

Evaluation of the improvement in effect for the two drugs

In the literature two factors are used with respect to the evaluation of the medicinal treatment of osteoporosis. The first is the probability for at least one new fracture during a three year period (called p) and the other is the mean intensity rate for fractures per year (called λ). Criticism has been raised in Windeler & Lange (1995) on the use of (mean) intensity rate. It is our belief that this argument is *not* convincing enough to discard analysis based on this parameter. The advantage of such an analysis is that one can also say something about the drugs ability to prevent repeated fractures in the same person. A further advantage is less uncertainty due to additional data. A disadvantage to the use of such data is, however, that stronger model assumptions must be made in order to study the mean intensity rate of fractures in relation to studying the probability for at least one fracture. Furthermore, the comparison of several studies necessitates the introduction of an assumption on a type of "likeness" in the different studies with respect to the parameters we intend to investigate (see below). From the standpoint of the data material, these assumptions seem more reasonable for the probabilities p than for the intensities λ. Given that there are both advantages and disadvantages in studying these two parameters, we intend to look at both.

The basis for analysis of etidronat are the studies of Storm et al. (1990) and Harris et al. (1993), while for alendronat we have the studies of Liberman et al. (1995) and Black et al. (1996). Table 2.1 summarises the results that have been produced in these studies.

We begin by looking at each of the drugs separately. In order to assess the studies combined, it is necessary to make at least one of the following two assumptions:

- The relative improvement in efficiency of the drug is the same for all levels of prevalence.
- The prevalence in the studies under consideration are equal.

The former is not an unusual assumption to make. Under this assumption it is possible to conduct an analysis of all studies combined, yielding more certain results than analyses of

	Studies	X		m		Y		n	
		P	D	P	D	P	D	P	D
etidronat	Storm	–	–	–	–	25*	9*	60.0*	54.0*
	Harris	32	28	184	196	71	52	606.6	604.4
alendronat	Liberman	22	17	355	526	40*	22*	1065.0	1578.0
	Black	145	78	965	981	240	86	2880.0	2928.0

Table 2.1: Data derived from Storm et al. (1990), Harris et al. (1993), Liberman et al. (1995) and Black et al. (1996). X is the number of patients with fractures, m is the total number of patients, Y is the total number of vertebral fractures, n is the total number of patient years, P = placebo, D = drug. A – indicates that data are unavailable, * indicates that data cannot be found directly, but are calculated from the data available in the articles.

individual studies. An initial analysis of the data gives the impression that this is not an unreasonable assumption to make.

The latter assumption will be incorrect if we look at all the studies. However, in the studies of Harris et al. (1993) and Black et al. (1996) this assumption does not seem unreasonable, and a direct comparison of etidronat and alendronat based on these studies alone is possible.

2.1 Parameters of assessment

Assume that we are assessing one study. Define

p_1 =the probability of at least one fracture in the course of 3 years when placebo is used;

p_2 =the probability of at least one fracture in the course of 3 years when the study drug is used.

and

λ_1 =the intensity of vertebral fracture per year when placebo is used;

λ_2 =the intensity of vertebral fracture per year when the study drug is used.

Table 2.2 shows estimates for the p's and λ's based on estimation methods from classical statistics. Of special interest is the fact that it appears that both the p's and λ's for the control (placebo) groups vary between the different studies. Notice also that the estimates of p for these groups in the studies of Harris et al. (1993) and Black et al. (1996) are similar as mentioned above.

We will study both the absolute and the relative (percent) improvement of p_2 compared to p_1 and λ_2 compared to λ_1. We define

$$\theta = p_1 - p_2, \qquad \phi = \lambda_1 - \lambda_2$$

	Studies	Estimate for p Placebo	Drug	Estimate for λ Placebo	Drug
etidronat	Storm	-	-	0.417	0.167
	Harris	0.165	0.143	0.117	0.086
alendronat	Liberman	0.062	0.032	0.038	0.014
	Black	0.150	0.080	0.083	0.029

Table 2.2: Estimates of the probability of at least one vertebral fracture in the course of three years and of annual intensity of vertebral fracture.

as parameters for absolute improvement, while

$$\alpha = (p_1 - p_2)/p_1, \qquad \beta = (\lambda_1 - \lambda_2)/\lambda_1$$

are parameters for relative improvement. Based on the data in Table 2.1, we can calculate estimates of these parameters. These are shown in Table 2.3. These results give an impression of the improvement attributable to the drug. However, the estimates give no impression of the degree of uncertainty.

	Estimate for Studies	θ	α	ϕ	β
etidronat	Storm	-	-	0.25	0.60
	Harris	0.02	0.13	0.03	0.26
alendronat	Liberman	0.03	0.48	0.02	0.63
	Black	0.07	0.47	0.05	0.65

Table 2.3: Estimates of improvement and relative improvement of the probability of at least one vertebral fracture in the course of 3 years, and of annual intensity of vertebral fracture.

2.2 Analyses of individual studies

With the model assumptions of Appendix A as a starting point, it is possible to calculate the posterior probability distribution for the improvement in effect of the p's (the probability of at least one fracture in the course of three years) and the λ's (the intensity of vertebral fracture per year). These distributions describe the uncertainty connected to the parameters true values based on data from the actual studies. The knowledge of the parameters true values *before* the data is considered non-informative. Figure 2.1 shows the posterior distributions for θ (the absolute improvement in p) for the different studies (Storm et al. (1990) is not included here due to lacking data). Table 2.4 summarises these distributions. In this, and later tables, quantities as defined by $\Pr(\theta > a|D)$ are given. $\Pr(\theta > a|D)$ refers to the "probability that θ is larger than a based on data D". D will

Drug	Studies	$\Pr(\theta > a\|D)$ $a =$	0.00	0.02	0.04	0.06	0.08	0.10
etidronat	Harris		0.79	0.61	0.40	0.21	0.09	0.03
alendronat	Liberman		0.98	0.75	0.26	0.03	0.00	0.00
	Black		1.00	1.00	0.98	0.77	0.26	0.02

Table 2.4: Summary of the posterior distributions for θ (absolute improvement of probability for at least one fracture in the course of three years) based on the different studies. The distributions are given in Figure 2.1. D refers to data from the actual studies.

Drug	Studies	$\Pr(\alpha > a\|D)$ $a =$	0.00	0.15	0.30	0.45	0.60	0.75
etidronat	Harris		0.79	0.55	0.24	0.04	0.00	0.00
alendronat	Liberman		0.98	0.94	0.82	0.56	0.19	0.01
	Black		1.00	1.00	0.98	0.60	0.02	0.00

Table 2.5: Summary of the posterior distributions for α (relative improvement in probability for at least one fracture in the course of three years) for the different studies. The distributions are given in Figure 2.2. D refers to data from the actual studies.

in this case be the data that are available from the actual study, while there will be data from additional studies once they are combined. All the studies give some indication of improvement. Notice also that even though the posterior distribution for θ in the study of Harris et al. (1993) is centered on the same improvement value as the study of Liberman et al. (1995), there is much more uncertainty associated with the former.

A similar analysis for α, the relative improvement in probability for at least one vertebral fracture in the course of three years, yields the posterior distributions in Figure 2.2. A summary of these posterior distributions is given in Table 2.5. Uncertainty in the study of Harris et al. (1993) is still present. At the same time note that the distributions of the relative improvement are centered on about the same value for the two alendronat studies, which again strengthens the possible assumption that the relative improvements are constant for different populations.

Turning our attention to intensities, we will first examine ϕ, the absolute improvement. Figure 2.3 illustrates posterior distributions for the four studies, while Table 2.6 summarises these distributions. The study of Storm et al. (1990) gives an indication of much larger absolute improvement than the other studies. This study has, however, a considerable amount of uncertainty attached to it due to the low number of patients.

The relative improvement in intensity, β, is summarised in Figure 2.4 and Table 2.7. Once again we see that the assumption of constancy among relative improvement seems reasonable for the two alendronat studies. For the two etidronat studies the posterior distributions for the relative improvement are centered on slightly different values. Uncer-

Drug	Studies	$\Pr(\phi > a\|D)$ $a =$	0.00	0.02	0.04	0.06	0.08	0.10
etidronat	Storm		0.99	0.99	0.98	0.97	0.96	0.94
	Harris		0.96	0.73	0.31	0.06	0.00	0.00
alendronat	Liberman		1.00	0.70	0.01	0.00	0.00	0.00
	Black		1.00	1.00	0.98	0.17	0.00	0.00

Table 2.6: Summary of the posterior distributions for ϕ (absolute improvement in intensity of vertebral fracture per year) for the different studies. The posterior distributions are shown in Figure 2.3. D refers to the data from the actual studies.

Drug	Studies	$\Pr(\beta > a\|D)$ $a =$	0.0	0.2	0.4	0.6	0.8	1.0
etidronat	Storm		0.99	0.97	0.87	0.52	0.05	0.00
	Harris		0.96	0.68	0.14	0.00	0.00	0.00
alendronat	Liberman		1.00	1.00	0.97	0.62	0.01	0.00
	Black		1.00	1.00	1.00	0.85	0.00	0.00

Table 2.7: Summary of the posterior distributions for β (relative improvement in intensity of vertebral fracture per year) for the different studies. The posterior distributions are shown in Figure 2.4. D refers to the data from the actual studies.

tainty in these studies is, however, large[1] even though the probability that the improvement based on the study of Storm et al. (1990) is greater than the improvement based on the study of Harris et al. (1993) is 0.93.

It is possible to conclude, based on a combined analysis of Tables 2.4-2.7, that there is evidence of a clear effect of both drugs in the reduction of the number of vertebral fractures in women with osteoporosis, however, alendronat is the better of the two.

2.3 Combined analysis of studies with the same drug

A direct comparison of investigations is difficult since the prevalences of osteoporosis are not the same in the populations selected in these different studies. The analyses in the previous section gave some indication that it would be reasonable to assume that the relative improvement based on the use of the drugs is not dependent on prevalence. In this section, the analysis will therefore be based on combining data from Storm et al. (1990) and Harris et al. (1993) and combining data from Liberman et al. (1995) and Black et al.

[1]Note that the uncertainty in β is approximately the same for the two etidronat studies, even though the Harris et al. (1993) study is considerably larger. This is a result of the fact that the intensity for the control group in this study is much smaller than in Storm et al. (1990). When this intensity is incorporated into the denominator in the definition of β, the smaller value results in increased uncertainty.

	$\Pr(\alpha > a\|D)$					
Studies	$a =$ 0.00	0.02	0.04	0.06	0.08	0.10
Liberman	0.98	0.94	0.82	0.56	0.19	0.01
Black	1.00	1.00	0.98	0.60	0.02	0.00
Combined	1.00	1.00	1.00	0.68	0.00	0.00

Table 2.8: Summary of the posterior distributions for α (relative improvement in the probability for at least one fracture in the course of three years) based on the two alendronat studies taken separately and combined. The posterior distributions are shown in Figure 2.5. D refers to the data from the actual stud(y)ies.

(1996). The methodology is outlined in Appendix A.2.

There is currently only one study available based on the drug etidronat with respect to the relative improvement of the probability for at least one fracture in the course of three years, α. An analysis of a combination of studies of α is therefore of interest only for alendronat. Figure 2.5 shows the posterior distributions for α based on the two available studies of alendronat, with a corresponding summary of data in Table 2.8. Both the distributions based on analyses of the studies taken separately and combined are shown. The posterior distributions for the two studies taken separately were centered on approximately the same value. Notice that the combination of studies causes a considerable reduction in the degree of uncertainty (in that the posterior distribution is more centered).

The same type of analysis can be performed for the relative improvement in intensity, β. Now it is also possible to combine the studies for the drug etidronat. For the etidronat studies the posterior distributions are shown in Figure 2.6, while the summaries for the posterior distributions are given in Table 2.9. In the case presented here, the central points in the distributions from the two studies taken separately are quite different, yet there is considerable overlap between the posterior distributions thus leaving no basis to conclude that the relative improvements are different in the two studies. A combination of the two studies nevertheless leads to a new central point as a mean of the original central points. In addition uncertainty is reduced.

For the alendronat studies the same distributions are shown in Figure 2.7, and summaries of the distributions are given in Table 2.10. Notice again the considerable improvement in the level of uncertainty.

Based on a combined analysis of Tables 2.8-2.10, it can be concluded that both drugs are effective in reducing the number of vertebral fractures among women with osteoporosis, alendronat being the better of the two.

2.4 Comparing studies of different drugs.

Here we will compare directly the two drugs based on the analysis in the previous section. If we continue to base ourselves on the assumption that the relative improvement of either the

		$\Pr(\beta > a\|D)$					
Studies	$a =$	0.0	0.2	0.4	0.6	0.8	1.0
Storm		0.99	0.97	0.87	0.52	0.05	0.00
Harris		0.96	0.68	0.14	0.00	0.00	0.00
Combined		1.00	0.98	0.43	0.00	0.00	0.00

Table 2.9: Summary of the posterior distribution for β (relative improvement in the intensity of vertebral fracture per year) based on the two etidronat studies taken separately and combined. The posterior distributions are shown in Figure 2.6. D refers to the data from the actual stud(y)ies.

		$\Pr(\beta > a\|D)$					
Studies	$a =$	0.0	0.2	0.4	0.6	0.8	1.0
Liberman		1.00	1.00	0.97	0.62	0.01	0.00
Black		1.00	1.00	1.00	0.85	0.00	0.00
Combined		1.00	1.00	1.00	0.91	0.00	0.00

Table 2.10: Summary of the posterior distribution for β (relative improvement in the intensity of vertebral fracture per year) based on the two alendronat studies taken separately and combined. The posterior distributions are shown in Figure 2.7. D refers to the data from the actual stud(y)ies.

probability for at least one fracture in the course of three years or the intensity of vertebral fracture per year is constant, it is then possible to analyse the differences between the two drugs. Two measures of improvement with alendronat compared to etidronat will be assessed:

$$\kappa_1 = \alpha_a - \alpha_e,$$
$$\kappa_2 = \beta_a - \beta_e,$$

an index a denotes alendronate, whereas e denotes etidronate. The first is a measure of the difference in the relative improvement of the probability for at least one fracture in the course of three years, while the second measures the difference in the relative improvement of the intensity of vertebral fractures per year. Figure 2.8 illustrates the posterior distributions for these parameters, while a summary of the distributions is given in Table 2.11. The studies of Harris et al. (1993), Liberman et al. (1995) and Black et al. (1996) were used for the calculation of posterior distribution for κ_1. For κ_2, the study of Storm et al. (1990) was also included.

An alternative approach is to ignore the assumption that the improvement in effect is independent of the prevalence of osteoporosis. In this case it is then necessary to compare studies in which the prevalences are approximately equal, as in the case of Harris et al. (1993) and Black et al. (1996) . We can assess this assumption by comparing the control

	$\Pr(\kappa > a\|D)$					
Studies	$a =$ 0.00	0.15	0.30	0.45	0.60	0.75
κ_1	0.96	0.79	0.50	0.23	0.09	0.03
κ_2	1.00	0.92	0.31	0.02	0.00	0.00

Table 2.11: Summary of the posterior distributions for κ_1 and κ_2 based on all four studies. The posterior distributions are shown in Figure 2.8. D refers to the data from the actual studies.

groups in the two studies. The left plot in Figure 2.9 illustrates the posterior distribution of the difference between the probabilities for at least one fracture in the course of three years among patients in the control groups of Harris et al. (1993) and Black et al. (1996). The mean of 0.027 is not that different from 0, and the data do not give a basis to conclude that the two groups are different. The 95% credibility interval is $[-0.030, 0.089]$[2].

Correspondingly, it is also possible to compare the intensities. The plot to the right in Figure 2.9 illustrates the posterior distribution for the difference between the intensities in the control groups of Harris et al. (1993) and Black et al. (1996). In this case the data give a clear indication that there is a difference between the two populations (the probability that the intensity in the Harris et al. (1993) study is larger than that observed in the study of Black et al. (1996) is 0.999; a 95% credibility interval for the difference is $[0.046, 0.235]$). The expectation in the posterior distribution is 0.137. Based on this analysis, an assumption that the two population are alike is more questionable. This is also indicated in Table 2.2, where the estimates for λ in the control groups for the two studies are less alike.

Based on the analyses of the control groups in the studies of Harris et al. (1993) and Black et al. (1996), it is possible to make a more direct comparison of the drugs by comparing the absolute improvements of the probabilities for at least one fracture in the course of three years for the two drugs. Let θ_a be the absolute improvement in the alendronat study of Black et al. (1996), while θ_e is the absolute improvement in the etidronat study of Harris et al. (1993). Figure 2.10 shows the posterior distribution of $\theta_a - \theta_e$ based on the data from the two studies, while Table 2.12 summarises this distribution. The probability that θ_a is larger than θ_e is 0.84, again indicating that use of alendronat results in a larger improvement than does use of etidronat; however the uncertainty here is somewhat larger than it would be had we based results on a larger number of studies.

Once again, based on a combined assessment of Tables 2.11 and 2.12 it is possible to conclude that alendronat is more effective than etidronat in reducing the number of vertebral fractures among women with osteoporosis.

[2]It is possible to perform a comparable analysis using classical statistics. The normal approximation can be used if the samples from both groups are large. A 95% confidence interval for the difference between the two probabilities is (-0.033, 0.081) (the p level for the hypothesis is 0.415), which again indicates that there is no essential difference between the two populations.

	$\Pr(\theta_a - \theta_e > a \mid D)$						
Studies	$a =$	0.00	0.01	0.02	0.03	0.04	0.05
$\theta_a - \theta_e$		0.84	0.77	0.69	0.60	0.50	0.40

Table 2.12: Summary of the posterior distribution for $\theta_a - \theta_e$ based on the studies of Harris et al. (1993) and Black et al. (1996). The posterior distributions are shown in Figure 2.10. D refers to the data from the actual studies.

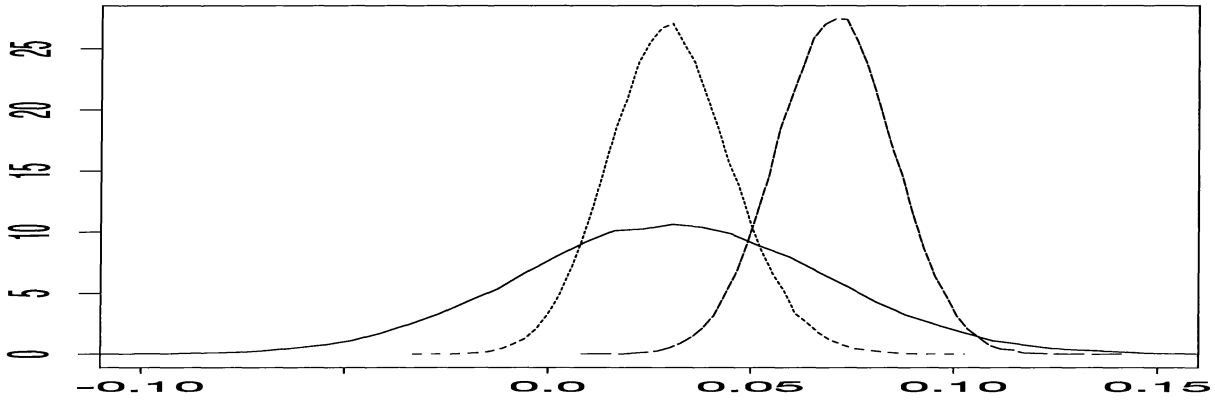

Figure 2.1: Posterior density for θ (the absolute improvement of the probability for at least one fracture in the course of three years) for the different studies. The solid curve shows the distribution based on the study of Harris et al. (1993), the dotted curve shows the distribution based on the study of Liberman et al. (1995), while the broken curve shows the distribution according to the study of Black et al. (1996).

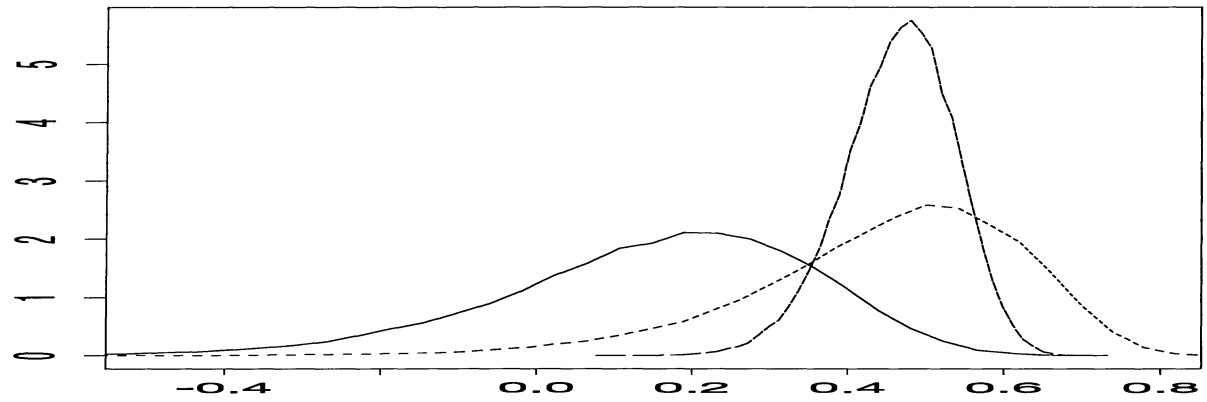

Figure 2.2: Posterior density for α (the relative improvement of the probability for at least one fracture in the course of three years) for the different studies. The solid curve shows the distribution based on the study of Harris et al. (1993), the dotted curve shows the distribution based on the study of Liberman et al. (1995), while the broken curve shows the distribution according to the study of Black et al. (1996).

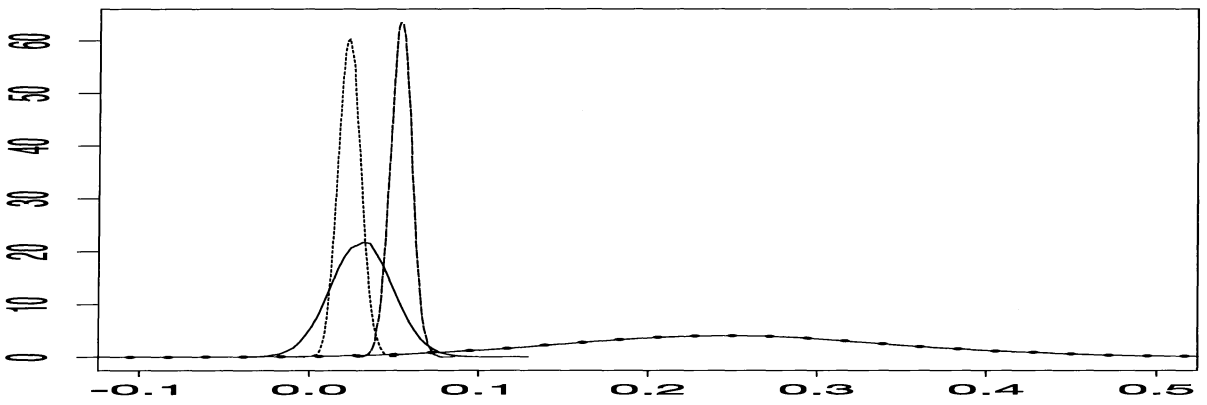

Figure 2.3: Posterior density for ϕ (the absolute improvement of intensity of vertebral fracture per year) for the different studies. The point-line curve shows the distribution based on the study of Storm et al. (1990), the solid curve shows the distribution based on the study of Harris et al. (1993), the dotted curve shows the distribution based on the study of Liberman et al. (1995), while the broken, narrow curve shows the distribution according to the study of Black et al. (1996).

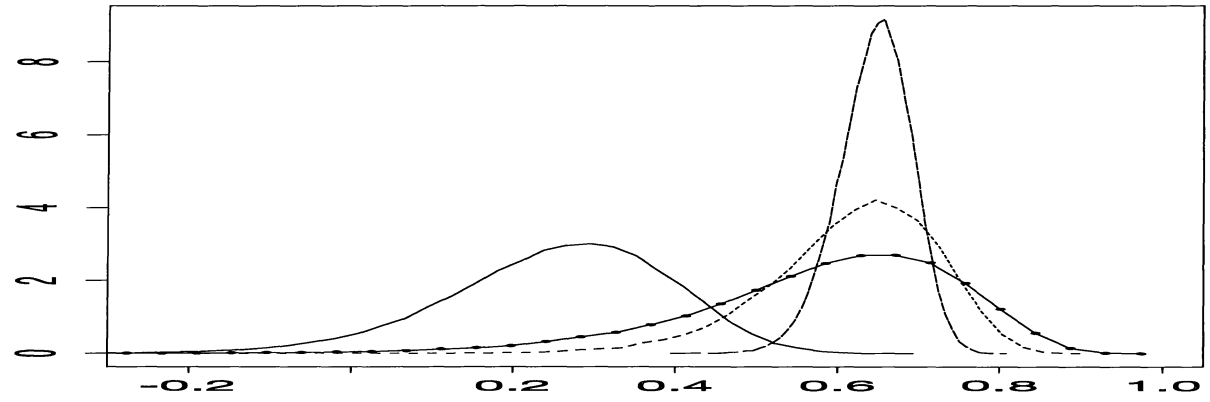

Figure 2.4: Posterior density for β (the relative improvement of intensity of vertebral fracture per year) for the different studies. The point-line curve shows the distribution based on the study of Storm et al. (1990), the solid curve shows the distribution based on the study of Harris et al. (1993), the dotted curve shows the distribution based on the study of Liberman et al. (1995), while the broken, narrow curve shows the distribution according to the study of Black et al. (1996).

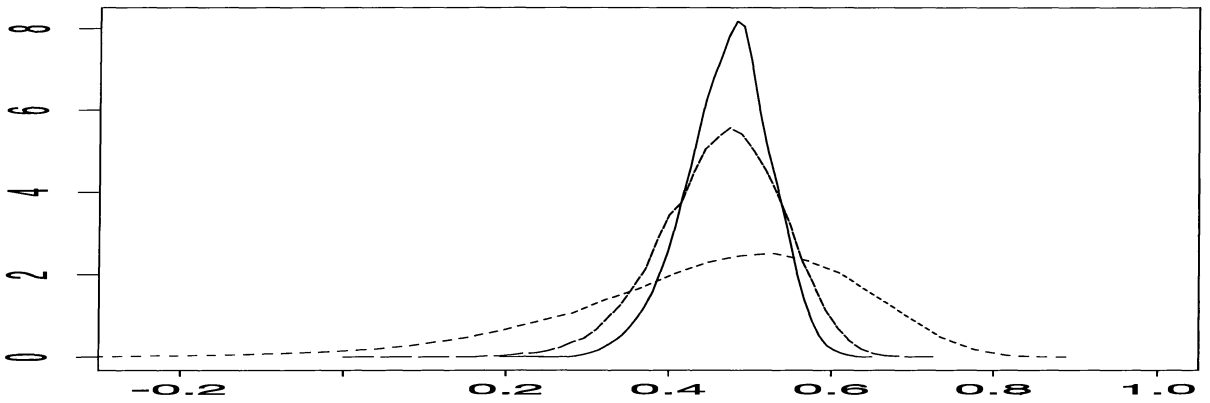

Figure 2.5: Posterior density for α (the relative improvement of the probability for at least one fracture in the course of three years) based on the studies of Liberman et al. (1995) (dotted curve) and Black et al. (1996) (broken curve) and the two studies combined (solid curve).

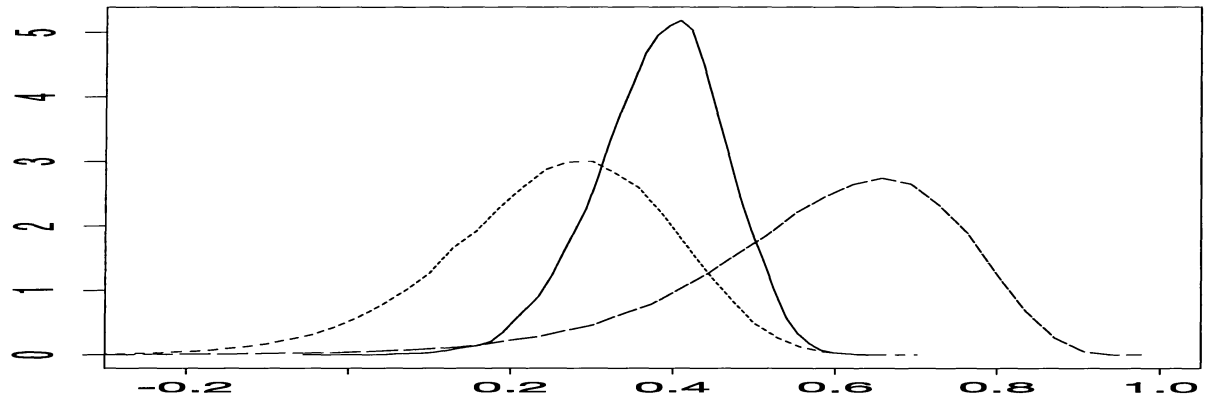

Figure 2.6: Posterior density for β (the relative improvement of the intensity of vertebral fracture per year) based on the studies of Storm et al. (1990) (dotted curve) and Harris et al. (1993) (broken curve) and the two studies combined (solid curve).

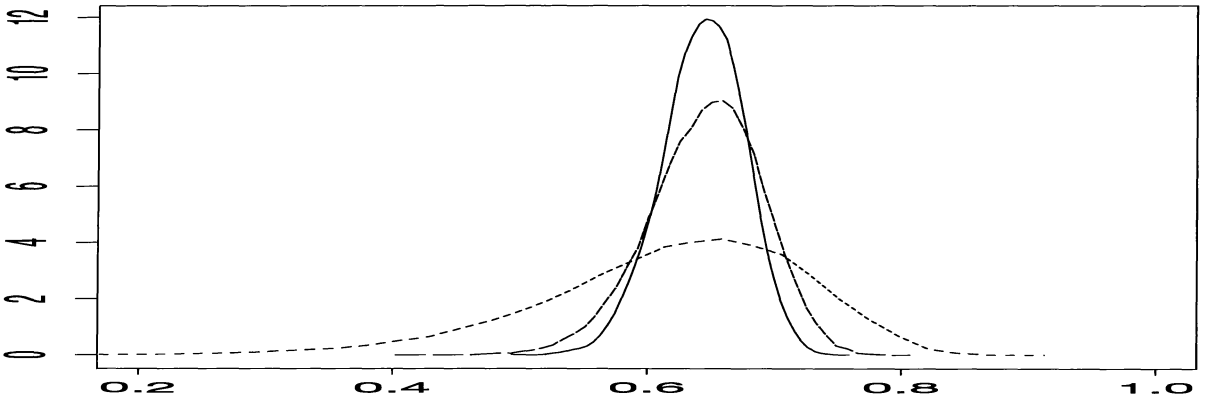

Figure 2.7: Posterior density for β (the relative improvement in the intensity of vertebral fracture per year) based on the studies of Liberman et al. (1995) (dotted curve) and Black et al. (1996) (broken curve) and the two studies combined (solid curve).

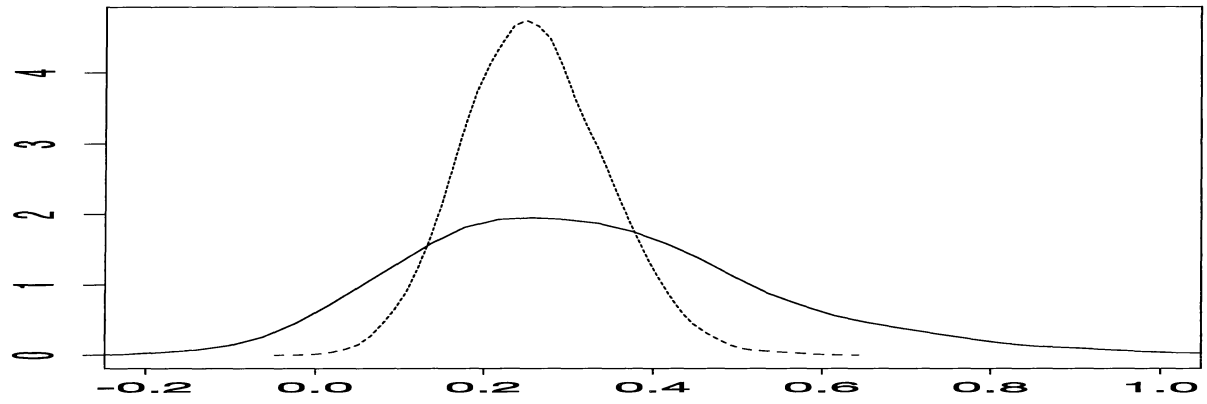

Figure 2.8: Posterior density for κ_1 (solid curve) and κ_2 (broken curve) based on all four studies.

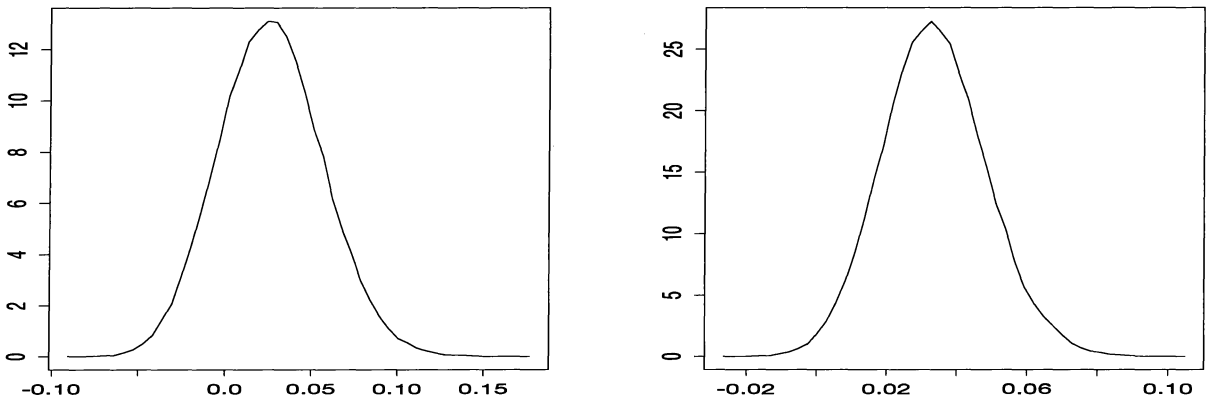

Figure 2.9: Posterior density for the difference between the probabilities for at least one fracture in the course of three years (left) and the difference between the intensities of vertebral fractures per year (right) in the control groups in the studies of Harris et al. (1993) and Black et al. (1996).

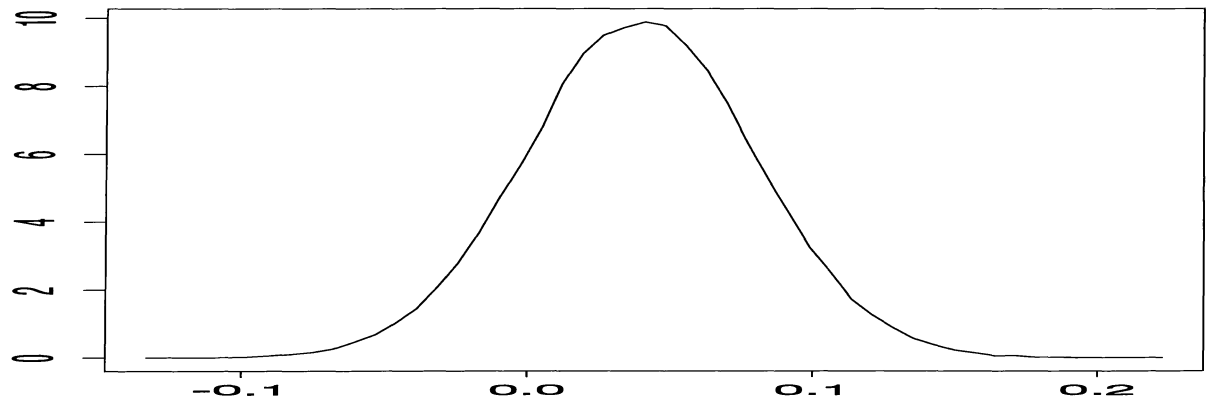

Figure 2.10: Posterior distributions for $\theta_a - \theta_e$ based on the studies of Harris et al. (1993) and Black et al. (1996)

Chapter 3

Analysis of costs

Table 3.1 shows the expected number of hip fractures over a three year period per 1000 women between the ages of 65 and 68 years with different levels of bone density. These values are derived through the use of the regression model presented in Gardsell et al. (1993). The annual intensities can be calculated by dividing these intensities by three. We will however calculate the costs for a three year period directly; freeing us from the assumption that the fracture intensities are the same (constant) each year.

A cost analysis of the two drugs will be carried out based on these data. Costs will be assessed with respect to the reduction in the number of hip fractures. The two drugs will also result in the reduction of other types of fractures (e.g. wrist fractures and vertebral fractures), thereby further reducing expenses through the treatment of osteoporosis. Expenses associated with these fractures are, however, difficult to estimate and have thus been excluded from this analysis. It is important to note also that alendronat will give larger improvement in the form of a larger reduction in the number of fractures of different types. A comparison of etidronat and alendronat will therefore result in a price estimation of alendronat that may be too low.

The expenses associated with the use of etidronat are set at 3000 NOK for a three year period. With respect to the costs of treating a hip fracture, the analyses have been carried out for various amounts in the neighborhood of 165,000 NOK (Andersen et al. (1995)). Costs for alendronat will be estimated by equating the expenses associated with the use of this drug to expenses associated with the use of etidronat.

The studies we have based our calculations on assess the number of vertebral fractures, not the number of hip fractures. In order to proceed with a cost analysis, the following assumption must be made:

> *The relative improvement in the intensity resulting from the use of a drug is the same for hip fractures as for vertebral fractures.*

Black et al. (1996) gives data for the relative improvement of the number of patients with at least one hip fracture, and arrives at an estimate of 0.5 (calculated from data in Table 3 in Black et al. (1996)), which is very close to the estimate for the relative improvement for

Bone density, SD	-1.0	-1.5	-2.0	-2.5	-3.0	-3.5
Fracture per 1000	10.9	13.9	17.6	22.3	28.1	35.3

Table 3.1: The expected number of fractures per 1000 patients for different bone densities. The bone density values are the number of standard deviations below the mean density of younger women. Numbers are for women aged from 65 years, taken over a three year period.

vertebral fractures, 0.47 (see Table 2.3). This is a number based on probabilities, and not on intensities which is of interest in this case; however, it does indicate that the assumption is not altogether unreasonable. Black et al. (1996) also includes data for wrist fractures of comparable magnitude (the relative improvement in the probability for at least one fracture in the course of a three year period is estimated to be 0.47). We will concentrate on hip fractures alone.

Under the assumption above we can use the analyses performed in the previous chapter to calculate uncertainty distributions (posterior distributions) for expected expenses. If λ is the intensity of hip fractures in the course of three years for patients who do not receive any drug, and β is the relative improvement in effect in using a drug, then $\lambda(1-\beta)$ will be the intensity of hip fractures for patients who receive the drug. The reduction in intensity is then $\lambda\beta$ and the reduction in expenses in connection with fractures over a three year period is:

$$\lambda\beta \times \text{the cost of one fracture.}$$

To determine the total costs, this reduction must be subtracted from the costs of using the drug, such that the total cost, K_r, is:

$$K_r = \text{ Cost of the drug} - \lambda\beta \times \text{the cost of one fracture,}$$

where "the cost of the drug" is the total cost associated with the use of the drug over a three year period.

The analyses in the previous chapter laid the basis for the assumption that the relative improvement in effect was approximately the same for the two alendronat studies. The same was, however, not true for the etidronat studies. We will, therefore, first concentrate on the study of Harris et al. (1993) for etidronat (since this is the largest study), while we will use both of the alendronat studies.

We begin with an estimation of the costs for alendronat. Table 3.2 shows estimates for the different costs per fracture. Initially, if one assumes that treatment is only relevant for groups with the highest intensity rates, a price 40 - 70 % higher than the price for etidronat could be considered reasonable for alendronat, possibly higher still if the costs of fractures are large.

Figure 3.1 shows posterior distributions for expenses for the two drugs for a cost per fracture of 165,000 NOK, and a treatment cost of 4,500 NOK for alendronat. An attempt is made to fix the price for alendronat such that the posterior distributions for the expenses associated with the use of etidronat and alendronat are centered on approximately the

	Intensity rates					
Cost per fracture	10.9	13.9	17.6	22.3	28.1	35.3
NOK 100'	3419	3534	3676	3857	4080	4357
NOK 120'	3502	3641	3811	4028	4296	4628
NOK 140'	3586	3748	3947	4200	4512	4899
NOK 160'	3670	3854	4082	4371	4728	5171
NOK 180'	3754	3961	4217	4543	4944	5442
NOK 200'	3838	4068	4353	4714	5160	5714

Table 3.2: Estimated prices for alendronat that give the same expenses as etidronat for different levels of intensity. Based on the studies of Harris et al. (1993), Liberman et al. (1995) and Black et al. (1996)

	Intensity rates					
Cost per fracture	10.9	13.9	17.6	22.3	28.1	35.3
NOK 100'	3284	3362	3458	3581	3732	3919
NOK 120'	3340	3434	3550	3697	3878	4103
NOK 140'	3397	3507	3642	3813	4025	4287
NOK 160'	3454	3579	3733	3929	4171	4471
NOK 180'	3511	3651	3825	4045	4317	4655
NOK 200'	3568	3724	3917	4162	4464	4839

Table 3.3: Estimated costs for alendronat that yield the same expenses as for etidronat for different levels of intensity. Based on all four studies.

same value for a bone density of 2.5 standard deviations below the mean (fourth plot in the figure), which is the definition of osteoporosis. Note that the uncertainty, particularly connected to costs in using etidronat, is large.

The analyses in the previous chapter gave indications that a combination of the two etidronat studies could be doubtful. We will, nonetheless, perform such an analysis. The results of this analysis can then be seen as the results for a type of "mean population" between the two studies. In this case, the estimated prices for alendronat are given in Table 3.3. Note that the prices are estimated lower here, due to a larger improvement in the Storm et al. (1990) study than the Harris et al. (1993) study which results in a smaller difference between the two drugs. A price approximately 30% higher for alendronat compared to etidronat seems reasonable in this case. Figure 3.2 shows posterior distributions for the expenses based on 165,000 NOK for the cost per hip fracture and 4,000 NOK for the price of alendronat. Once again, this price is fixed in order to equalise the levels of bone density at 2.5 standard deviations under the mean (forth plot in the figure).

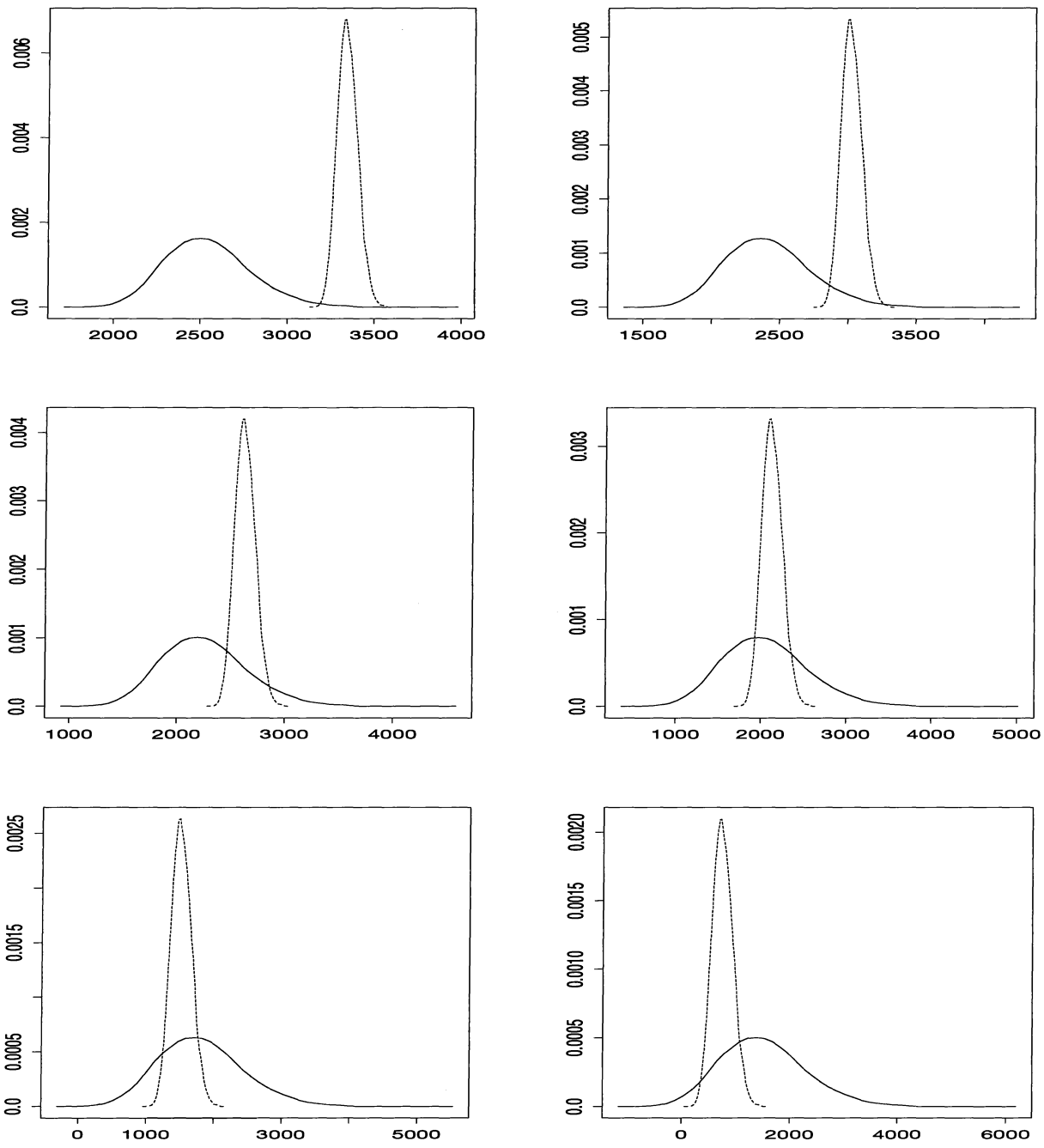

Figure 3.1: Posterior distributions for expenses associated with the use of etidronat (solid curve) and alendronat (broken curve). Top left represents bone density 1.0, top right represents bone density 1.5 standard deviations below normal; followed by bone densities of 2.0, 2.5, 3.0 and 3.5 standard deviations below normal. The costs for alendronat are fixed at 4,500 NOK for a three year period. The results are based on the studies of Harris et al. (1993), Liberman et al. (1995) and Black et al. (1996).

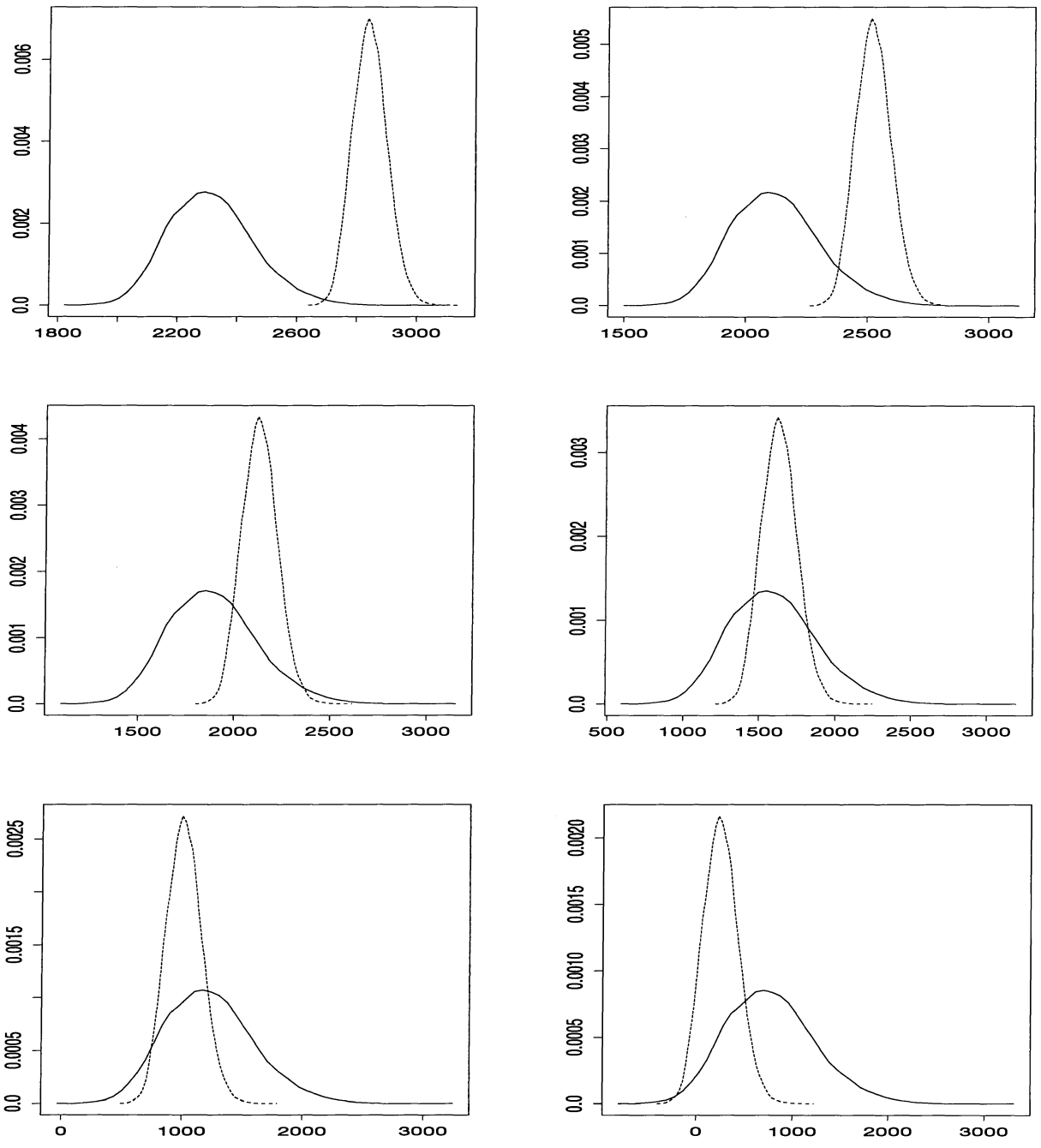

Figure 3.2: Posterior distributions for expenses associated with the use of etidronat (solid curve) and alendronat (broken curve). Top left represents bone density 1.0, top right represents bone density 1.5 standard deviations below normal; followed by bone densities of 2.0, 2.5, 3.0 and 3.5 standard deviations below normal. The costs for alendronat are fixed at 4,000 NOK for a three year period. The results are based on all four studies.

Appendix A

Model assumptions and methodological basis

In this appendix we will present the mathematical assumptions and methods that are used for the calculation of the different posterior distributions. The basis for the construction of posterior distributions lies in the use of Bayes formula (or theorem). Let q be the parameter of interest, and let D be the available data. If we define $\pi_0(q)$ as the prior distribution of q and let $f(D|q)$ be the likelihood for the data if q is the true value of the parameter, then the posterior distribution of q (given D) is:

$$\pi(q|D) = \frac{\pi_0(q)f(D|q)}{\int_{q'} \pi_0(q')f(D|q')dq'}. \tag{A.1}$$

In many cases (and in the situation presented in this paper), it will be reasonably simple to set up the analytic equation for the numerator in (A.1), while the denominator (which is only a proportionality constant that ensures that the posterior distribution has a total mass of 1) is often unknown or in practice impossible to calculate.

It is, however, possible to simulate from the actual posterior distributions. The computer can make a sample $\{q^1, ..., q^M\}$ from the posterior distribution. An estimate for the density of the posterior probability can thus be constructed by making a density estimate based on the samples. In the current paper we have made use of a standard kernel density estimate.

Furthermore, for a comparison of two parameters, q_1 and q_2, the use of a simulation technique will be very practical. If one is, for example, interested in the absolute difference between these two variables, a sample from the posterior distribution of this difference can be derived directly by $\{q_2^1 - q_1^1, ..., q_2^M - q_1^M\}$ where $\{(q_1^1, q_2^1), ..., (q_1^M, q_2^M)\}$ are samples from the posterior distribution of (q_1, q_2).

The use of simulation with respect to exact calculations will add an additional uncertainty factor to the results. In practise, this uncertainty factor will be negligible if M is reasonably large. We have used an $M = 100,000$ in our calculations. A sensitivity analysis based on a repetition of the calculations many times shows that this is adequate.

In the next section we present a short overview of the models that are used and describe the resulting posterior distributions. For those cases in which there are no standard results, deductions of the posterior distributions are also included.

A.1 Analysis of each stage

Assume that we are assessing one study. Define

p_1 =the probability of at least one fracture in the course of 3 years when placebo is used;

p_2 =the probability of at least one fracture in the course of 3 years when the study drug is used.

Note that we make an assumption that the probabilities are alike for all individuals (in the populations under study). This is not necessarily true, since patients will vary dependent on age, bone density etc. With the available data this assumption is, however, absolutely necessary. In principle this refers to allowing the above probabilities to be a type of "mean probability" over the study population.

We define

X_1 =the number of patients with at least one fracture in the course of three years when placebo is used;

X_2 =the number of patients with at least one fracture in the course of three years when the study drug is used.

Let m_1 and m_2 be the total number of patients in the placebo and medication groups respectively. If we assume that there is independence among patients, then

X_1 will be binomially distributed with m_1 attempts and a probability of success of p_1;

X_2 will be binomially distributed with m_2 attempts and a probability of success of p_2.

The Bayesian approach is based on the construction of probability distributions for p_1 and p_2. This does not mean that these parameters are to be interpreted as random, but our knowledge of the parameters is uncertain and we describe this uncertainty with the help of probability distributions. Such probability distributions are called *prior distributions.*

In principle it is now possible to build in a great deal of information about p_1 and p_2 in the prior distributions. This information will however be subjective. In order to be as objective as possible, we will assume that the probability distributions for p_1 and p_2

are uniform (rectangularly distributed) over the interval $[0, 1]$. This agrees with omitting information on the probabilities in the prior distributions.

When we then consider the observed data D, the prior distributions are updated to *posterior distributions*, denoted by $\pi(p_1|D)$ and $\pi(p_2|D)$. It is these distributions that are the basis for the Bayesian statistical inference. In this case D will be the observations X_1 and X_2. This leads to (see Berger (1985)))

$$\pi(p_1|D) \sim \text{Beta}(1 + X_1, 1 + m_1 - X_1) \tag{A.2}$$
$$\pi(p_2|D) \sim \text{Beta}(1 + X_2, 1 + m_2 - X_2), \tag{A.3}$$

i.e. p_1 and p_2 have Beta-distributions as posterior distributions, with parameters dependent on the data that are observed.

The analysis of fracture intensity will be similar. Define

λ_1 =the fracture intensity per year when placebo is used;

λ_2 =the fracture intensity when the study drug is used.

Further define:

Y_1 =total number of fractures in the course of three years when placebo is used;

Y_2 =total number of fractures in the course of three years when the study drug is used.

Let n_1 and n_2 be the total number of patients in the placebo and drug groups respectively. We will then assume that:

Y_1 is Poisson distributed with the intensity $n_1\lambda_1$;

Y_2 is Poisson distributed with the intensity $n_2\lambda_2$.

The assumption of Poisson distribution is somewhat stronger than the assumption of binomial distribution of the X's, in that we say more about the shape of the probability distributions of the Y's. Note that in this case it is not necessary to assume that the intensities are the same for each person. Since the analysis makes use of the sum of vertebral fractures, it is enough that this is Poisson distributed with an intensity that is the sum of the individual intensities.

Also in this case, we wish that the analysis is as objective as possible and choose therefore an (almost) non-informative prior distribution for the parameters λ_1 and λ_2. We have chosen to begin with a uniform distribution over the interval $[0, \lambda_{max}]$. λ_{max} is the upper limit for the intensities λ_1 and λ_2. We have chosen $\lambda_{max} = 10$, but small trials with other values gave near identical results. The posterior distributions for the λ's are thus:

$$\pi(\lambda_1|D) \sim Gamma_{tr}(Y_1, n_1, \lambda_{max}) \tag{A.4}$$
$$\pi(\lambda_2|D) \sim Gamma_{tr}(Y_2, n_2, \lambda_{max}), \tag{A.5}$$

where $Gamma_{tr}$ is the *truncated* Gamma distribution, truncated above λ_{max}.

A.2 Combining studies of the same drug.

By analysing individual studies, we will get several probability distributions each of which must be assessed in order to say anything conclusive about the drug overall. It would be advantageous therefore to combine studies for analysis (for an analysis of etidronat, the studies of Storm et al. (1990) and Harris et al. (1993) could be combined, while a combined analysis of alendronat would include the studies of Liberman et al. (1995) and Black et al. (1996)).

A direct combination of the studies is difficult since the prevalences of osteoporosis will be different for the populations sampled in the different studies. In order to proceed an assumption is necessary. Within a study, define

$$\alpha = (p_1 - p_2)/p_1,$$

i.e. α is a measure of the relative improvement effect (in the form of the number with at least one fracture in the course of three years) in relation to the control group for the relevant study. The assumption we make is that the relative improvement in effect *is not dependent on the population that is sampled*, but dependent only on the choice of drug. We will still choose the non-informative prior distributions used earlier, but will in this case build into the model that the relative improvement in effect is the same for the studies that are combined.

A similar combination can be used for the analysis of fracture intensities. Define

$$\beta = (\lambda_1 - \lambda_2)/\lambda_1,$$

i.e. the relative improvement of fracture intensities. Here we will build in an assumption that the β's are the same for studies of the same drug.

The next two sections will deal with the calculations of posterior distributions for α and β respectively.

A.2.1 Probabilities for at least one fracture in the course of three years

Assume for study i,

$X_{1,i}$ =the number of patients with at least one fracture in the course of three years in the placebo group;
$m_{1,i}$ =the total number of patients in the placebo group;
$X_{2,i}$ =the number of patients with at least one fracture in the course of three years in the drug group;
$m_{2,i}$ =the total number of patients in the drug group.

We assume as before that $X_{1,i} \sim Bin(m_{1,i}, p_{1,i})$, while $X_{2,i} \sim Bin(m_{2,i}, p_{2,i})$. The likelihood for the X's is then

$$f(x_{1,1}, ..., x_{2,S}) = \prod_{i=1}^{S} \begin{pmatrix} m_{1,i} \\ x_{1,i} \end{pmatrix} p_{1,i}^{x_{1,i}} (1 - p_{1,i})^{m_{1,i} - x_{1,i}} \begin{pmatrix} m_{2,i} \\ x_{2,i} \end{pmatrix} p_{2,i}^{x_{2,i}} (1 - p_{2,i})^{m_{2,i} - x_{2,i}} \tag{A.6}$$

As before, we will use the uniform (rectangular) distribution over the interval $[0, 1]$ as prior distributions for both $p_{1,i}$ and $p_{2,i}$. We will at the same time assume that the relative improvement of the drug is constant in the different studies, i.e.

$$\alpha = (p_{1,i} - p_{2,i})/p_{1,i}, \qquad i = 1, ..., S;$$

where S is the number of studies of the drug in question. In practise we will therefore have only $S + 1$ free parameters, $p_{1,1}, ..., p_{1,S}$ and α. We are then required to specify the simultaneous prior distribution for these parameters. We will assume that this distribution is of the form

$$\pi(\alpha, p_{1,1}, ..., p_{1,S}) = \pi(\alpha) \prod_{i=1}^{S} \pi(p_{1,i}|\alpha),$$

i.e., for a given α, the $p_{1,i}$'s are independent. Furthermore, we maintain that if we look at one study only $p_{1,i}$ and $p_{2,i}$ will be independent and both uniformly distributed. This puts demands on $\pi(\alpha)$ and $\pi(p_{1,i}|\alpha)$. In particular, when $(p_{1,i}, \alpha)$ can be interpreted as a transformation of $(p_{1,i}, p_{2,i})$, we are required to have (from the normal rules of transformation)

$$\pi(p_{1,i}, \alpha) = p_{1,i}.$$

If we know $\pi(\alpha)$, we can find $\pi(p_{1,i}|\alpha)$ by

$$\pi(p_{1,i}|\alpha) = \frac{\pi(p_{1,i}, \alpha)}{\pi(\alpha)}.$$

We will therefore begin by determining what distribution α must have in order that $p_{1,i}$ and $p_{2,i}$ are independent and uniformly distributed for each of the studies. The sample space of α is $[-\infty, 1]$. To find the prior distribution of α, assume first that $k > 0$. Then

$$\begin{aligned}
\Pr(\alpha \leq k) &= \int_0^1 \Pr(\alpha \leq k|p_{1,i}) dp_{1,i} \\
&= \int_0^1 \Pr(p_{2,i} \geq (1 - k)p_{1,i}|p_{1,i}) dp_{1,i} \\
&= \int_0^1 [1 - (1 - k)p_{1,i}] dp_{1,i} \\
&= [1 - (1 - k)\frac{1}{2}] \\
&= \frac{1}{2}[1 + k]
\end{aligned}$$

Further , for $k \leq 0$,

$$\begin{aligned}
\Pr(\alpha \leq k) &= \int_0^1 \Pr(\alpha \leq k|p_{1,i})dp_{1,i} \\
&= \int_0^1 \Pr(p_{2,i} \geq (1-k)p_{1,i}|p_{1,i})dp_{1,i} \\
&= \int_0^{1/(1-k)} [1-(1-k)p_{1,i}]dp_{1,i} \\
&= [\frac{1}{1-k} - (1-k)\frac{1}{2(1-k)^2}] \\
&= \frac{1}{2(1-k)}
\end{aligned}$$

i.e.

$$\Pr(\alpha \leq k) = \frac{1}{2}\begin{cases} \frac{1}{1-k} & k \leq 0 \\ 1+k & k > 0 \end{cases}$$

and

$$\pi(\alpha) = \frac{1}{2}\begin{cases} \frac{1}{(1-\alpha)^2} & \alpha \leq 0 \\ 1 & \alpha > 0 \end{cases}$$

We also have

$$\pi(p_{i,1}|\alpha) = 2p_{1,i}\begin{cases} (1-\alpha)^2 & \text{if } \alpha \leq 0, \\ 1 & \text{if } \alpha > 0; \end{cases}$$

(note that this is only true for $p_{1,i} \leq \min\{1, 1/(1-\alpha)\}$, otherwise it will be 0) and finally

$$\pi(\alpha, p_{1,1}, ..., p_{1,S}) = \begin{cases} (1-\alpha)^{2(S-1)} 2^S \prod_{i=1}^S p_{1,i} & \text{if } \alpha \leq 0, \\ 2^S \prod_{i=1}^S p_{1,i} & \text{if } \alpha > 0; \end{cases} \tag{A.7}$$

for $\max_i p_{1,i} \leq \min\{1, 1/(1-\alpha)\}$. By putting this together with the likelihood function (A.6), we have the *simultaneous* posterior distribution of $(p_{1,1}, ..., p_{1,S}, \alpha)$ given by

$$\begin{aligned}
&\pi(\alpha, p_{1,1}, ..., p_{1,S}|D) \\
&\quad \propto \prod_{i=1}^S p_{1,i}^{x_{1,i}+1}[1-p_{1,i}]^{m_{1,i}-x_{1,i}} \times \\
&\quad \prod_{i=1}^S [(1-\alpha)p_{1,i}]^{x_{2,i}}[1-(1-\alpha)p_{1,i}]^{m_{2,i}-x_{2,i}} \times \\
&\quad \begin{cases} (1-\alpha)^{2(S-1)} & \text{if } \alpha \leq 0 \\ 1 & \text{if } \alpha > 0 \end{cases}
\end{aligned} \tag{A.8}$$

for $\max_i p_{1,i} \leq \min\{1, 1/(1-\alpha)\}$ and 0 otherwise.

The distribution (A.8) is neither simple to calculate nor to simulate. One method that can be used for simulating from this distribution is the Sampling/Importance Resampling (SIR) algorithm (Rubin (1987), Tanner (1993)).

This is based on the fact that we know the posterior distributions of the $p_{1,i}$'s for each individual study. If we then simulate values from these distributions, we get "reasonably good" estimates of the $p_{1,i}$'s. We can also find "reasonably good" estimates for α by using a mean over the studies. The simulations will, however, not be exact. The SIR algorithm is a method for *weighting* the simulations that have been done and thereafter performing new simulations based on these weights. Theoretical considerations grant that this yields near exact results if the number of simulations performed is adequate.

A.2.2 Intensities of fractures

Let us now move to the intensities

$Y_{1,i}$ =the number of fractures in the placebo group for study i
$Y_{2,i}$ =the number of fractures in the drug group for study i

We assume $Y_{1,i} \sim \text{Poisson}(n_{1,i}\lambda_{1,i})$ while $Y_{2,i} \sim \text{Poisson}(n_{2,i}\lambda_{2,i})$. The likelihood for the Y's are in this case given by

$$f(y_{1,1}, ..., y_{2,S}) = \prod_{i=1}^{S} \frac{\lambda_{1,i}^{y_{1,i}} \exp(-\lambda_{1,i})}{y_{1,i}!} \cdot \frac{\lambda_{2,i}^{y_{2,i}} \exp(-\lambda_{2,i})}{y_{2,i}!} \tag{A.9}$$

We will assume that both $\lambda_{1,i}$ and $\lambda_{2,i}$ have a uniform prior distribution on the interval $[0, \lambda_{max}]$, which corresponds to an (almost) non-informative distribution. We will further assume that the relative improvement of the drug is constant in the different studies, i.e.

$$\beta = (\lambda_{1,i} - \lambda_{2,i})/\lambda_{1,i}, i = 1, ..., S;$$

where S is the number of studies of the drug in question. As for the p's, we will now have only $S+1$ free parameters that require the specification of a prior distribution. It is assumed that this has the form

$$\pi(\beta, \lambda_{1,1}, ..., \lambda_{1,S}) = \pi(\beta) \prod_{i=1}^{S} \pi(\lambda_{1,i}|\beta),$$

which results in a conditional independence among the $\lambda_{1,i}$'s. If we now choose that $\lambda_{1,i}$ and $\lambda_{2,i}$ have independent uniform distributions, each over the interval $[0, \lambda_{max}]$, we must in this case have

$$\pi(\lambda_{1,i}, \beta) = \frac{\lambda_{1,i}}{\lambda_{max}}.$$

The sample space of β is $[-\infty, 1]$. To find the prior distribution for β, assume first $\beta > 0$. Then

$$\begin{aligned}
\Pr(\beta \leq b) =& \int_0^{\lambda_{max}} \Pr(\beta \leq b|\lambda_{1,i}) \frac{1}{\lambda_{max}} d\lambda_{1,i} \\
=& \frac{1}{\lambda_{max}} \int_0^{\lambda_{max}} \Pr(\lambda_{2,i} \geq (1-b)\lambda_{1,i}|\lambda_{1,i}) d\lambda_{1,i} \\
=& \frac{1}{\lambda_{max}} \int_0^{\lambda_{max}} [1 - \frac{(1-b)\lambda_{1,i}}{\lambda_{max}}] d\lambda_{1,i} \\
=& \frac{1}{\lambda_{max}} [\lambda_{max} - \frac{1-b}{\lambda_{max}} \frac{\lambda_{max}^2}{2}] \\
=& \frac{1}{2}[1+b]
\end{aligned}$$

Further for $b \leq 0$,

$$\begin{aligned}
\Pr(\beta \leq b) =& \int_0^{\lambda_{max}} \Pr(\beta \leq b|\lambda_{1,i}) \frac{1}{\lambda_{max}} d\lambda_{1,i} \\
=& \frac{1}{\lambda_{max}} \int_0^{\lambda_{max}} \Pr(\lambda_{2,i} \geq (1-b)\lambda_{1,i}|\lambda_{1,i}) d\lambda_{1,i} \\
=& \frac{1}{\lambda_{max}} \int_0^{\lambda_{max}/(1-b)} [1 - \frac{(1-b)\lambda_{1,i}}{\lambda_{max}}] d\lambda_{1,i} \\
=& \frac{1}{\lambda_{max}} [\frac{\lambda_{max}}{1-b} - \frac{1-b}{\lambda_{max}} \frac{\lambda_{max}^2}{2(1-b)^2}] \\
=& \frac{1}{2(1-b)}
\end{aligned}$$

i.e.

$$\Pr(\beta \leq b) = \frac{1}{2} \begin{cases} \frac{1}{1-b} & b \leq 0; \\ 1+b & b > 0, \end{cases}$$

and

$$\pi(\beta) = \frac{1}{2} \begin{cases} \frac{1}{(1-\beta)^2} & \beta \leq 0; \\ 1 & \beta > 0. \end{cases}$$

And so we get

$$\pi(\lambda_{1,i}|\beta) = 2\frac{\lambda_{1,i}}{\lambda_{max}} \begin{cases} (1-\beta)^2 & \beta \leq 0; \\ 1 & \beta > 0, \end{cases}$$

for $\lambda_{1,i} \leq \lambda_{max} \min\{1, 1/(1-\beta)\}$ and 0 otherwise. By putting this together with the likelihood function (A.9), we have the simultaneous posterior distribution of $(\lambda_{1,1}, ..., \lambda_{1,S}, \beta)$ given by

$$\begin{aligned}
&\pi(\beta, \lambda_{1,1}, ..., \lambda_{1,S}|D) \\
&\qquad \propto \exp(-\sum_{i=1}^{S} n_{1,i}\lambda_{1,i} - (1-\beta)\sum_{i=1}^{S} n_{2,i}\lambda_{1,i})(1-\beta)^{\sum_{i=1}^{S} y_{2,i}} \prod_{i=1}^{S} \lambda_{1,i}^{y_{1,i}+y_{2,i}+1} \times \\
&\qquad \begin{cases} (1-\beta)^{2(S-1)} & \text{for } \beta \leq 0 \\ 1 & \text{for } \beta > 0 \end{cases}
\end{aligned} \tag{A.10}$$

The SIR algorithm can be used for simulating from this distribution also.

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