Chapter 3

The Basic Model

Modelling effect in multicenter studies is of interest and under investigate for quite some time [1]. This chapter presents the basic model for multicenter studies which has been developed by Böhning (2004).

For the data in the form of Table 1.1, let x_i^T denote the number of events in the treatment arm of the i-th center and n_i^T denote patients under risk in the treatment arm of the i-th center. Also let x_i^C denote the number of events in the control arm of the i-th center and n_i^C denote patients under risk in the control arm of the i-th center. Let the number of centers be k, so that $i = 1, \ldots, k$, and let p_i^T and p_i^C denote the risk (probability) of an event in the treatment and control arm, respectively.

3.1 Measurement of Treatment Effect

This study focuses on the measurement of treatment effect like the relative risk. The relative risk for each center can be defined as the risk of an event in the treatment arm divided by the risk of an event in the control arm [41].

$$\theta_i = p_i^T / p_i^C \tag{3.1}$$

where θ_i is the relative risk for the i-th center,

p_i^T is the risk of an event in the treatment arm, and

p_i^C is the risk of an event in the control arm.

Other effect measures are possible including the risk difference and the odds ratio. Here attention is on the relative risk since, for one, it is a very common effect measure in clinical trials, and, for two, the statistical treatment simplifies considerably.

3.2 Likelihood

In multicenter studies, the variation of the measurement of treatment effect, here the relative risk, between studies can be investigated. If homogeneity of treatment effect can be established, the results are more supportive of the treatment effect. If heterogeneity of treatment effect is present, an appropriate modelling is required and sources of heterogeneity should be investigated.

For each center and for each arm, there is a Poisson Likelihood, so that for the i-th center, the contribution to the likelihood of the treatment arm is

$$\exp(-n_i^T p_i^T)(n_i^T p_i^T)^{x_i^T}/x_i^T! \tag{3.2}$$

and for the i-th center, the contribution to the likelihood of the control arm is

$$\exp(-n_i^C p_i^C)(n_i^C p_i^C)^{x_i^C}/x_i^C!. \tag{3.3}$$

Then the product of the likelihood over *all* centers becomes

$$\prod_{i=1}^{k} \exp(-n_i^T p_i^T)(n_i^T p_i^T)^{x_i^T}/x_i^T! \times \exp(-n_i^C p_i^C)(n_i^C p_i^C)^{x_i^C}/x_i^C! \tag{3.4}$$

and the *log-likelihood* function can be written as:

$$\sum_{i=1}^{k} -n_i^T p_i^T + x_i^T \log(p_i^T) - n_i^C p_i^C + x_i^C log(p_i^C) \tag{3.5}$$

when we ignore the additive constants, independent of p_i^T and p_i^C.

3.3 Estimation of Relative Risk based upon the Basic Model

In order to estimate relative risk in multicenter studies, one can simply rewrite p_i^T as $p_i^C\theta_i$ and the log-likelihood function for estimating relative risk becomes

$$\sum_{i=1}^{k} -n_i^T p_i^C \theta_i + x_i^T \log(p_i^C \theta_i) - n_i^C p_i^C + x_i^C log(p_i^C). \tag{3.6}$$

Note that the log-likelihood function in equation (3.6) consists of two kinds of parameter. The first type is the parameter of interest, that is the relative risk θ_i. The second type is the nuisance parameter, that is the baseline parameter of the control group p_i^C. The

nuisance parameter is not our main parameter of interest, but it is a parameter that can give a complete description of the likelihood.

However, a potential overprecision in the estimator for the parameter of interest has been occured from apparently knowing the nuisance parameter as an explicit function of the data and the parameter of interest [2]. This problem is overcome by using a profile likelihood rather than a full likelihood [24].

3.4 The Concept of Profile Method

The concept of profile likelihood method is to concentrate the likelihood on a single parameter by eliminating the nuisance parameter [2, 24, 43]. The likelihood approach to eliminate a nuisance parameter is to replace the nuisance parameter by its maximum likelihood estimator at each fixed value of the parameter of interest. The result of this process is called the profile likelihood. The profile likelihood is then treated like a likelihood function of a low-dimensional parameter which can be used to a considerable extent as a full likelihood for the parameter of interest, for example, it is customary to use the curvature of the profile likelihood function as an estimate of the variability of parameter of interest [24, 43].

Let θ be the parameters of interest and ϕ be the nuisance parameters, and let $L(\theta, \phi)$ be the log-likelihood for arbitrary but fixed θ. Then the profile log-likelihood $L^*(\theta)$ is defined as

$$L^*(\theta) = L[\theta, \hat{\phi}(\theta)] \tag{3.7}$$

where $\hat{\phi}(\theta)$ is the maximum likelihood estimate (MLE) of ϕ for given θ.

Note that the profile log-likelihood now depends only on the parameter of interest and, thus, the method of profile log-likelihood can be viewed as a method which eliminates nuisance parameters.

3.5 The Profile Likelihood for the Relative Risk

In this section we determine the profile log-likelihood based on (3.6) which we now consider as a function of $\mathbf{p}^C$ for arbitrary, but fixed $\theta = (\theta_1, \ldots, \theta_k)'$.

$$L(\mathbf{p}^C|\theta) = \sum_{i=1}^{k} -n_i^T p_i^C \theta_i + x_i^T \log(p_i^C \theta_i) - n_i^C p_i^C + x_i^C \log(p_i^C) \tag{3.8}$$

To find the maximum likelihood estimates of $\mathbf{p}^C$ for given θ, we calculate the partial derivatives

$$\frac{\partial}{\partial p_j^C} L(\mathbf{p}^C|\theta) = \frac{\partial}{\partial p_j^C} \sum_{i=1}^{k} -n_i^T p_i^C \theta_i + x_i^T \log(p_i^C \theta_i) - n_i^C p_i^C + x_i^C \log(p_i^C) \tag{3.9}$$

$$\begin{aligned} &= \frac{\partial}{\partial p_j^C} \sum_{i=1}^{k} -(n_i^T \theta_i) p_i^C + x_i^T \log(p_i^C) + x_i^T \log(\theta_i) - n_i^C p_i^C + x_i^C \log(p_i^C) \\ &= -n_j^T \theta_j + x_j^T / p_j^C - n_j^C + x_j^C / p_j^C \end{aligned}$$

and then set them to zero to get MLE of p_j^C as

$$p_{j\theta}^C = \frac{x_j^C + x_j^T}{n_j^C + n_j^T \theta_j}. \tag{3.10}$$

By inserting (3.10) into (3.8) we achieve that

$$\sum_{i=1}^{k} -(n_i^C + \theta_i n_i^T)(\frac{x_i^C + x_i^T}{n_i^C + \theta_i n_i^T}) + x_i^T \log(\theta_i) + (x_i^C + x_i^T) \log(\frac{x_i^C + x_i^T}{n_i^C + \theta_i n_i^T}) \tag{3.11}$$

which simplifies to

$$\sum_{i=1}^{k} -(x_i^C + x_i^T) + x_i^T \log(\theta_i) + (x_i^C + x_i^T) \log(x_i^C + x_i^T) + (x_i^C + x_i^T) \log(n_i^C + \theta_i n_i^T). \tag{3.12}$$

Finally, the *profile log-likelihood* for the risk ratio will be

$$L^*(\theta) = \sum_{i=1}^{k} x_i^T \log(\theta_i) - (x_i^C + x_i^T) \log(n_i^C + \theta_i n_i^T) \tag{3.13}$$

when only parameter dependent terms are considered.

This idea of using the profile likelihood in connection with the relative risk leading to the simple likelihood (3.13) has been suggested in Böhning (2004) and will now be used in the next chapter to incorporate the modelling of covariate information.