Adjusting for Non-compliance in Screening Trials

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It is conventional to analyse randomised trials according to the treatment of option assigned to each patient - the so-called intent-to-treat (ITT) method. The dangers of excluding non-compliant patients or analysing a trial according to actual treatment are well recognised (Altman 1991, p. 461-71), and can lead to biases which undermine the original reasons for randomisation. The ITT approach can lead to substantial under-estimate of the value of treatment, when applied to individual patients who are compliers.

By extending an approach used by Sommer & Zeger (1991), we previously developed a method for evaluating the effect of a new treatment which adjusted for refusal to accept the new treatment (non-compliance) and off protocol use of the treatment in controls (contamination). This approach fully respects the randomisation, but allows an unbiased estimate of the value of treatment in those patients who are prepared to accept it (Cuzick *et al*, 1997). With this method the magnitude of the treatment effect is usually larger than that found by ITT methods, but the confidence intervals are also longer, so that asymptotic power levels are the same. An additional advantage is that more realistic confidence intervals are provided, which is particularly important for trials aimed at showing the equivalence of two treatments.

It is convenient to think of the trial population as composed of three classes of individuals:

1. Insistors: Demand the new treatment no matter which group they are randomised to,
2. Ambivalent: Accept whichever treatment they are offered, and
3. Refusers: Refuse the new treatment, if offered.

Each of these classes is split at random to receive the new treatment (Treatment A) or the conventional treatment (Treatment B or Control). The statistical difficulties arise because it is not always possible to determine which (latent) class individuals belong to. Thus, only 4 groups can be directly observed from the data:

I. Insistors (Class 1) randomised to Treatment B (Control).
II. Ambivalent and Refusers (Classes 2 & 3) randomised to Treatment B (Control).
III. Insistors and Ambivalents (Classes 1 & 2) randomised to Treatment A.
IV. Refusers (Class 3) randomised to Treatment A.

One use of this methodology is to adjust estimates of screening efficacy obtained from non-randomised studies to allow for differences in baseline risk of compliers and non-compliers to invitation. Typically these analyses are done on a case-control basis and tend to over-estimate the benefits of screening. This approach has been developed for breast cancer screening by mammography in Duffy *et al.* (2001). If ψ is the unadjusted odds ratio, p is the proportion participating in screening and D_r is the disease specific mortality in non-compliers compared to compliers, then the corrected odds ratio for the whole population (intent-to-treat analysis) is

$$RR_1 = D_r(p\psi + 1 - p)$$

and the odds ratio for compliers is

$$RR_2 = \frac{p\psi D_r}{1 - (1-p)D_r}.$$

To use these formulae, one needs an independent estimate of D_r, which can be obtained from the randomised trials. Values obtained from 5 trials will be presented. They are quite consistent and give an overall estimate of 1.36. Thus, non-compliers are estimated to have an intrinsically 36% higher death rate than compliers. This will be used to adjust the estimates from non-randomised studies in Dalarna, Sweden and Florence, Italy.

A further theoretical development is to extend this approach to the proportional hazards model for time-to-event data. In our previous paper we indicated a somewhat *ad hoc* approach based on stratification of time intervals. Robins and Tsiatis (1991) and others have developed methods based on accelerated failure models. However, the most widely used method for analysing clinical trials with time-to-event as an endpoint is based on the proportional hazards model (Cox, 1972), and it would seem desirable to extend this standard method to deal with non-compliance and contamination.

Let α_j denote the proportion of the population belonging to class j, $j = 1, 2, 3$, $\lambda_j^{(t)}, \Lambda_j(t)$ be the hazard and cumulative hazard functions in the absence of treatment for $j = 2, 3$ and in the presence of treatment for $j = 1$ (insistors). Let $f_j(t)$, $S_j(t)$ be the corresponding density and survivor functions. Let $v \equiv v_{ik}$ be the indicator function for the ith subject being in class 2 ($k = 2$) and being randomised to the new treatment and $z = (z_1, \ldots, z_m)$ be any other covariates. Finally let δ_i be the indicator for subject i being an observed failure time (zero corresponding to a censored observation). The basic model then postulates that an individual with covariates (ν, z) will have hazard

$$e^{\beta_0 \nu + \beta z} \lambda_j(t).$$

Note that the treatment effect is only apparent for patients in class 2 and that ν is not an observable covariate. For insistors (class 1), all patients receive treatment regardless of the

randomised allocation so the treatment effect can be absorbed into the baseline hazard. Also, no patients in class 3 receive treatment.

A likelihood can be formed as a product of terms, with one for each individual; $L = \prod_i L_i$, where L_i takes different forms according to the observed group in which the patient lies:

I Control Insistors:

$$L_i = \theta_i^{\delta_i} \lambda_1^{\delta_i}(t_i) e^{-\theta_i \Lambda_1(t_i)}$$

where

$$\theta_i = \exp(\beta z_i) = \exp(\beta_1 z_{1i} + \ldots + \beta_m z_{mi})$$

II Control - Ambivalent and Refusers combined:

$$L_i = \theta_i^{\delta_i} \left[\frac{\alpha_2 \lambda_2^{\delta_i}(t_i) e^{-\theta_i \Lambda_2(t_i)} + \alpha_3 \lambda_3^{\delta_i}(t_i) e^{-\theta_i \Lambda_3(t_i)}}{\alpha_2 + \alpha_3} \right]$$

III Treated - Insistors and Ambivalent:

$$L_i = \theta_i^{\delta_i} \left[\frac{\alpha_1 \lambda_1^{\delta_i}(t_i) e^{-\theta_i \Lambda_1(t_i)} + \alpha_2 \theta_{0i}^{\delta_i} \lambda_2^{\delta_i}(t_i) e^{-(\theta_{0i}+\theta_i)\Lambda_2(t_i)}}{\alpha_1 + \alpha_2} \right]$$

where $\theta_{0i} = \exp(\beta_0 z_{0i})$.

IV Allocated Treatment - Refusers:

$$L_i = \theta_i^{\delta_i} \lambda_3^{\delta_i}(t_i) e^{-\theta_i \Lambda_3(t_i)}$$

Note that the only place that the treatment effect explicitly occurs ($v_i = 1$) is for group III where it is found in the term corresponding to the Treated Ambivalent.

In this generality the likelihood is difficult to analyse and considerable simplification occurs if we assume that non-compliers and contamination affect the likelihood in a proportional way, ie.

$$\lambda_j(t) = e^{\gamma_j w_j} \lambda(t)$$

where w_j is the indicator for membership in class j. For identifiability we take $\gamma_2 \equiv 0$ so that $\lambda(t) \equiv \lambda_2(t)$.

Estimation proceeds by partialling out the baseline hazard in a manner similar to that used for the traditional proportional hazard model, with separate local estimates of the α_k, and then using standard likelihood methods.

Further details and simulations will be presented to demonstrate the accuracy of point and interval estimates.

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RESUME

Non-compliance to allocated treatment can have a major impact on the results of trials. It reduces power and also will bias estimates towards the null. The former cannot be recovered, but methods exist for adjusting estimates for non-compliance in a way which respects the randomisation procedure. Applications are given for interpreting breast screening trials and programmes, and some new methods are developed to handle time-to-event data.

Le non respect des traitements prescripts peut avoir un impact majeur sur les resultats des essais cliniques. Cela reduit le 'power' et biaise les estimations vers zero. L'effet sur le premier ne peut etre corrige, mais des methodes qui respectent le procede de randomisation existent pour adjuster les estimations en case de non respect des traitements. Des applications existent aussi pour interpreter les essais et programmes de depistage de cancer du sein et de nouvelles methods ont ete developpees pour traiter les informations en function du temps de latence.