LATENT EVENTS IN CLINICAL TRIALS: A MODEL WITH SURE OUTCOMES OF RANDOM EVENTS*

by

A. Bouckaert** **and M. Mouchart*****

Abstract

A stochastic model of drug versus placebo parallel arms clinical trial with binary outcomes is given in this paper. The model takes into account for therapeutic and adverse effects. These effects are manifest but their dependence on latent effects is made explicit. The model obtained can be used to discriminate between direct and indirect toxic effects of drug administration. Several hierarchically embedded models are considered so that the choice of the best one can be made by likelihood ratio tests. The model can also be designed to accommodate a dose effect relationship.

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**Faculty of Medecine and Institute of Statistics, Université catholique de Louvain, Belgium.
***CORE and Institute of Statistics, Université catholique de Louvain, Belgium.
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1 Introduction

The clinical trial is accepted today as the standard way of establishing the usefulness of a new therapy, including the use of a new drug. By "usefulness", however, we understand not only that patients health will improve to a greater extent but also that the new therapy will cause them no harm. The detection of side effects and of a possible causal relation between a new drug and such side effects is thus a routine part of therapeutic experimentation. Many obstacles are met in the way of obtaining reliable estimations of safety for a new drug, e.g. quoting Finney (1982): "*Clinical trials adequate to demonstrate the efficacy of a drug or its superiority to previous remedies for the same condition will not be large enough to detect an increased frequency of agranulocytosis or cataract formation at a rate of 1 in 1000 or 1 in 10 000*".

In this study, our endeavour will be to develop and formalize ideas first expressed by Bernheim and Vrana (1995) about the relation between therapeutic activity and side effect occurrence. In their study, the authors suppose that the occurrence of side effects has at least three causes: [1] the pharmacologic properties of the drug, [2] toxic placebo (=nocebo) effects, [3] the pathology of the patient himself. For example, cough will be observed in patients treated for bronchial diseases, first because cough is a symptom of the illness, second because (possibly) the process of medical supervision stimulates cough (perhaps because expectorant syrups are prescribed or because the patient is more interested in recording his own symptomatology or because the perception of cough by the physician is more sensitive), and finally because (possibly) the test drug stimulates cough. The action of the drug can then be considered as either direct (as in the latter case) or indirect (through the action of the drug on bronchitis). In this study, we will try to discriminate between direct and indirect actions. This example and other considerations on the subject suggest that it would be an advantage to consider effects as determined by one, or several, among a set of possible but hidden causes. A statistical model (we call it "sure outcome of random events" or SORE model)

will be developped to meet this objective. This model will then be compared to more traditional approaches.

The word "placebo" is often used with different meanings: in particular, the "placebo" group is a group of patients receiving an inert preparation (also called "placebo"), without active drug. In order to avoid ambiguities in the future, this group is called the "control" group. All therapeutic or toxic effects manifested by these patients are thus "placebo" effects. This does not imply that placebo effects occur only in the "control" group. Their occurrence is just equally likely in the "drug" group. The therapeutic and toxic "placebo" effects are assumed to be unrelated, having only in common the fact that they do not depend on drug presence and are not affected by it.

The placebo effect is an instance of residual effect. It explains that part of the outcome that is not explained by the pharmacological properties of the drug. Two aspects should be stressed. First, the two effects can be simultaneous. Second, in most situations of clinical trials, the pharmacological action of a drug is not directly observable because, for instance, this would require the visualization of molecular processes.

2 The SORE Model: an outline

In a deterministic model, an "effect" (health improvement or adverse event) is always attributable to one single cause. Consider however somebody who is eager to cross the Channel and decides to do so if and only if a free ticket is available to him. Suppose there is is a probability α for him of receiving a free boat ticket and a probability β of receiving a free ticket for the shuttle. Obviously, if we learn, later on, that he crossed the Channel, he made the trip by sea or by rail but not both. (We discard the possibility of air travel to preserve the simplicity of this example).

Let us introduce three binary variables: X, Y and Z defined as follows: $\{Y = 0\}$ for the event "channel not crossed" and $\{Y = 1\}$ for the complementary event

"channel crossed"; in a similar way, $\{X = 0\}$ for "no free sea ticket" and $\{Z = 0\}$ for "no free rail ticket". The (almost sure) relation between the outcome Y and the random variables X and Z is given by:

$$Y = X + Z - XZ \tag{2.1}$$

This almost sure relation between binary variables is called here a "Sure Outcome of Random Events" model (SORE). Note that (2.1) may also be interpreted as saying that the event indicated by Y is equivalent to the union of the events indicated by X and Z respectively.

This model clearly implies:

$$P(Y = 1) = E(Y) = E(X + Z - XZ) \tag{2.2}$$

If, in addition, X and Z are independent and if we define $\alpha = E(X)$ and $\beta = E(Z)$, we obtain:

$$E(Y) = \alpha + \beta - \alpha\beta \tag{2.3}$$

A comparaison with the Logistic Model

Let us look again at the gentleman who contemplates to cross the Channel for holiday. Assume now that his decision will be encouraged by sunshine and by the wishes of his children. Specifically, if the sun does not shine ($X = 0$) and children prefer to stay home ($Z = 0$), he is unlikely to cross. The probability increases if the sun shines even if the children are reluctant. The probability increases even more if the sun shines *and* the children are enthusiastic.

This situation could be modelled by a saturated logistic model of the following type:

$$E(Y|x, Z) = \frac{e^{\beta_0+\beta_1 X+_2 Z+\beta_3 XZ}}{1 + e^{\beta_0+\beta_1 X+_2 Z+\beta_3 XZ}} \tag{2.4}$$

Could it not be assumed that the SORE model is just a special case of this logistic model? Note that in model (2.1), our gentleman would be *compelled* to cross the Channel as soon as the sun shines or that the children agree or both. In such a situation:

$$E(Y|X = 1, Z) = E(Y = 1|X, Z = 1) = 1 \tag{2.5}$$

$$E(Y|X=0,Z=0)=0 \tag{2.6}$$

This is an impossible behaviour for the logistic model: this is due to the (almost sure) relation (2.1).

3 A S.O.R.E. Model of the clinical trial

3.1 Basic concepts

Let us now consider the problem of modelling the main therapeutic effects (health improvement or not) and the side effects (or adverse events) observed during a clinical trial, when the possibility of placebo and nocebo effects is explicitly taken into account. Throughout this study, we assume that side reactions and health improvement are observed without errors, and that treatment allocations have been unblinded for the analysis.

To present the specifics of the model, we start by introducing two kinds of events, coded by means of binary variables defined at the level of individuals:

First, there are three "**observable**" **events**, namely :

Group allocation X, with $X = 0$ for the control group and $X = 1$ for the "drug" group.

Side effects, Y with $Y = 0$ for no side effects, $Y = 1$ for the occurrence of side effect.

Improvement Z, with $Z = 0$ for no health improvement, $Z = 1$ for health improvement.

Second, there are four "**non-observable**" **events**, namely:

Therapeutic pharmacological action λ, with $\lambda = 0$ for no action, $\lambda = 1$ for action; this is a physical process, for example the reaction between a molecule of drug and a receptor.

Toxic pharmacological action ν, with $\nu = 0$ for no action, $\nu = 1$ for (toxic) action; this is also a molecular process involving a drug-receptor interaction. The fact that ν is described here as "toxic" is actually immaterial to our model. The

important notion is that this action has a pharmacological basis, involving another drug-receptor interaction than λ.

Placebo therapeutic action θ, with $\theta = 0$ for no action, $\theta = 1$ for action. The nature of this "placebo" action (psychological, inert components of a tablet,etc.) is also immaterial to the model. Thus, placebo effect includes the "effect of time". The important notion is that this effect is not related to the presence of the molecules of the active drug. Its occurrence is thus unrelated to the fact that the patient belongs to the "placebo" group or to the "drug" group.

Placebo toxic (nocebo) action μ, with $\mu = 0$ for no action, $\mu = 1$ for action. Again, the nature of this effect is not important for the structure of the model, as long as it does not depend on the presence of the drug. It is also important that the "toxic" effects generated by μ and by ν are identical, in so far as they cannot be distinguished by observation.

Thus, those seven binary variables $(X, Y, Z, \theta, \lambda, \mu, \nu)$ take their values in a space with $2^7 = 128$ points.

The latent events $\theta, \lambda, \mu, \nu$ are included in the model because they correspond to well-known concepts in pharmacology and because they determine observable events in a SORE model framework. More specifically, note first that health improvement results from placebo effect, drug effect or both, i.e.:

$$Z = \theta + \lambda - \theta\lambda \tag{3.1.1}$$

Next, adverse reactions result from drug toxicity, placebo toxic reaction or both, i.e.:

$$Y = \mu + \nu - \mu\nu \tag{3.1.2}$$

Finally, the logic of the model implies two other deterministic constraints, namely that drug therapeutic effects are not possible unless drug is administered, i.e.:

$$\{\lambda = 1\} \Rightarrow \{X = 1\} \tag{3.1.3}$$

or, equivalently:

$$\lambda = \lambda X \qquad (3.1.3bis)$$

and similarly, drug toxic effects are not possible unless drug is administered, i.e.:

$$\{\nu = 1\} \Rightarrow \{X = 1\} \qquad (3.1.4)$$

or, equivalently:

$$\nu = \nu X \qquad (3.1.4bis)$$

Our model embodies now two SORE models, namely (3.1.1) and (3.1.2). For simplicity, this global model will also be called a SORE model.

Hypotheses

Next, we introduce a set of conditions of stochastic independence: these conditions formalize some structural properties of the problem. Firstly, we suppose, of course,that allocation of patients to groups is randomly realized from a homogeneous population. More specifically, we first assume:

$$\theta \underline{\parallel} X \qquad (3.1.5)$$

This means that placebo effects are independent of group assignment. We also assume:

$$\theta \underline{\parallel} \lambda | X \qquad (3.1.6)$$

This means that in each group of patients, pharmacologic and placebo effects are independent. Note however, as expressed in (3.1.3), that the pharmacologic effect is possible in the drug-treated patients only. Eventually, the two conditions (3.1.5) and (3.1.6) are jointly equivalent to:

$$\theta \underline{\parallel} (\lambda, X) \qquad (3.1.7)$$

Next, we assume that in each group the drug toxic reactions occur independently of placebo therapeutic or toxic effects and independently of the therapeutic effect of the drug; in other words, the probability of a drug toxic reaction depends only

of group allocation and given that one, it is the same whether there is a nocebo reaction or not; more precisely:

$$\nu \perp\!\!\!\perp (\mu, \theta, \lambda, Z)|X \tag{3.1.8}$$

Finally, we shall also assume that the probability of placebo toxic (= nocebo) effects depends only of health status improvement. Given that one, the probability of a nocebo effect is the same for all patients irrespectively of their group allocation and whatever the cause of the improvement or lack of improvement of their health. The dependence on Z is motivated in Bernheim and Vrana (1995) and corresponds to cause [3] in section 1; more precisely:

$$\mu \perp\!\!\!\perp (\theta, \lambda, X)|Z \tag{3.1.9}$$

Parametrization

All those constraints cooperate to reduce the dimensionality of the parameter space, as made explicit in Table I. More specifically, the independence hypotheses (3.1.5), (3.1.6), (3.1.8), (3.1.9) account respectively for 1, 1, 7 and 4 restrictions. The structural constraints (3.1.1) to (3.1.4) add a total of 108 restrictions, and one further restriction comes from probabilities summing to one. The full description of the model requires thus 128-13-108-1=6 free parameters.

Table I

Besides the known randomization parameter into the two treatment groups ($E(X) = Q$), five unknown parameters are necessary to specify the model. Given the restrictions explicited above, these parameters are suitably chosen as follows:

1. The probability of improvement by placebo reaction: $\beta = E(\theta)$
2. The probability of improvement by a pharmacologic action of the drug:

$$\alpha = E(\lambda|X = 1).$$

3. The probability of side effects by a placebo reaction in improved patients:

$$\eta = E(\mu|Z = 1)$$

4. The probability of side effect by a placebo reaction in unimproved patients:

$$\xi = E(\mu|Z = 0)$$

5. The probability of side effect by direct drug action: $\phi = E(\nu|X = 1)$.

Figure 1 gives a full description of all possible trajectories of this model. In this graph, square (resp. round) boxes are associated to observable (resp. non-observable) events. The graph can be concentrated on the trajectories of the observable events only, as is done in Figure 2.

Figures 1 and 2

Sampling

If we consider $\{(X_\ell, Y_\ell, Z_\ell) \quad \ell = 1 \dots n\}$ a simple random sample of size n generated by the complete SORE model, we define $N[ijk]$ as the number of patients observed in group $X = i$, with status $Z = j$ and $Y = k$, i.e.:

$$N[i, j, k] = \sum_{1 \le \ell \le n} \mathbf{1}_{\{X_\ell = i, Y_\ell = j, Z_\ell = k\}} \text{ with } i, j, k \in \{0, 1\}.$$

The data may be analyzed as a multinomial sampling from a three-way contingency table, the expectations of which are given in Table II.

Table II

The log-likelihood of the observations conditional on X, is given by:

$$\begin{aligned}
\log L = {} & N[000](\ln(1-\xi) + \ln(1-\beta)) + N[001](\ln(\xi) + \ln(1-\beta)) \\
& + N[010](\ln(\beta) + \ln(1-\eta)) + N[011](\ln(\beta) + \ln(\eta)) \\
& + N[100](\ln(1-\alpha) + \ln(1-\beta) + \ln(1-\phi) + \ln(1-\xi)) \\
& + N[101](\ln(1-\alpha) + \ln(1-\beta) + \ln(\phi + \xi - \xi\phi)) \\
& + N[110](\ln(\alpha + \beta - \alpha\beta) + \ln(1-\eta) + \ln(1-\phi)) \\
& + N[111] \ln(\alpha + \beta - \alpha\beta) + \ln(\phi + \eta - \phi\eta))
\end{aligned}$$

The Fisher information matrix and the m.l. estimates of the five parameters are given in the Appendix.

3.2 Comparison with the Logistic Model

In this section, we analyze the restrictions implied by a SORE model in comparison with a saturated model. The SORE model, defined in Section 3.1 on both latent and manifest variables, induces a multinomial model on the manifest variables as shown in Figure 2. A saturated model on the manifest variables would imply one parameter for $E(X)$ and six parameters for $E(Y, Z|X)$. In the conditional model implied by SORE, $E(Y, Z|X)$ is characterized by only 5 parameters: (α, β) characterizes $E(Z|X)$, and (η, ξ, ϕ) characterizes $E(Y|X, Z)$.

Let us consider a canonical parametrization of the saturated conditional model, namely:

$$\begin{aligned} E(Z|X=0) &= \beta \\ E(Z|X=1) &= \zeta \\ E(Y|X=0, Z=0) &= \xi \\ E(Y|X=0, Z=1) &= \eta \\ E(Y|X=1, Z=0) &= \gamma \\ E(Y|X=1, Z=1) &= \kappa \end{aligned} \tag{3.2.1}$$

Clearly, in the saturated model, the parameters are variation-free; more specifically

$$(\beta, \zeta, \eta, \xi, \gamma, \kappa) \in [0, 1]^6 \tag{3.2.2}$$

whereas in the SORE model:

$$(\alpha, \beta, \eta, \xi, \phi) \in [0, 1]^5 \tag{3.2.3}$$

The (over- and sub-)identification rests therefore on the properties of the transformation :

$$(\alpha, \phi) \leftrightarrow (\zeta, \gamma, \kappa) \text{ for given } (\beta, \eta, \xi) \tag{3.2.4}$$

We first note that:

$$\zeta = \alpha + \beta - \alpha\beta \tag{3.2.5}$$

This implies that the SORE model involves the following restriction on the canonical parameter space $[0,1]^6$:

$$\zeta \geq \beta \tag{3.2.6}$$

which means that the probability of health improvement is at least as high in the treated group as in the control group.
Next, the SORE model implies :

$$\kappa = \phi(1-\eta) + \eta \tag{3.2.7}$$

$$\gamma = \phi(1-\xi) + \xi \tag{3.2.8}$$

which requires that:

$$\begin{aligned} \kappa &\geq \eta \\ \gamma &\geq \xi \end{aligned} \tag{3.2.9}$$

along with

$$\frac{1-\eta}{1-\xi} = \frac{\kappa-\eta}{\gamma-\xi} \tag{3.2.10}$$

or equivalently

$$\kappa = \eta + \left(\frac{\gamma-\xi}{1-\xi}\right)(1-\eta) \tag{3.2.10bis}$$

Note that (3.2.10) may also be written as:

$$\frac{1-E(Y|X=0,Z=1)}{1-E(Y|X=0,Z=0)} = \frac{E(Y|X=1,Z=1)-E(Y|X=0,Z=1)}{E(Y|X=1,Z=0)-E(Y|X=0,Z=0)} \tag{3.2.11}$$

Restriction (3.2.9) means that whether there has been health improvement ($Z = 1$) or not ($Z = 0$), the probability of adverse effect is at least as high in the treated group as in the control group whereas restriction (3.2.10), or (3.2.11), is the characteristic restriction of the SORE model.

The SORE model is thus a multinomial model subject to the following restrictions, easily written in terms of the parametrization (3.2.2), namely:

(i) an exact restriction (3.2.10)

(ii) inequalities (3.2.6) and (3.2.9)

Thus, testing the SORE model against the saturated model boils down to testing restriction (3.2.10) in the conditional model generating $(Y|X,Z)$, along with the inequalities ensuring that the parameters of the saturated model lead to feasible values of the parameters of the SORE model.

The saturated model can also be specified by a logistic reparametrization as follows:

$$E(Y|X,Z) = \frac{e^{a+bX+cZ+dXZ}}{1+e^{a+bX+cZ+dXZ}} \tag{3.2.12}$$

with the following correspondences:

$$\begin{aligned} a &= \ln(\frac{\xi}{1-\xi}) \\ b &= \ln(\frac{\gamma(1-\xi)}{(1-\gamma)\xi}) \\ c &= \ln(\frac{\eta-\xi)}{(1-\eta)\xi}) \\ d &= \ln(\frac{\kappa(1-\gamma)\xi(1-\eta)}{(1-\kappa)\gamma(1-\xi)\eta}) \end{aligned} \tag{3.2.13}$$

Note that the logistic model *without interaction* i.e. with $d = 0$, implies the restriction:

$$\frac{(1-\eta)(1-\gamma)}{(1-\kappa)(1-\xi)} = \frac{\eta\gamma}{\kappa\xi} \tag{3.2.14}$$

Clearly, restriction (3.2.14), implied by the absence of interaction, is different from restriction (3.2.10) implied by the SORE model unless a further restriction is introduced, namely:

$$\eta\gamma = \kappa\xi \tag{3.2.15}$$

When adverse effects (Y) and health improvement (Z) are independent in each group (X) i.e.:

$$Y \perp\!\!\!\perp Z|X \tag{3.2.16}$$

or, equivalently

$$\eta = \xi \text{ and } \gamma = \kappa \tag{3.2.8bis}$$

restrictions (3.2.10), (3.2.14) and (3.2.15) are satisfied, i.e. at the level of $E(Y|X,Z)$, under (3.2.16) the SORE model is equivalent to the logistic model without interaction and both models may be written as:

$$E(Y|X,Z) = E(Y|X) = \frac{e^{a+bX}}{1+e^{a+bX}} = \gamma X + \xi(1-X) \tag{3.2.17}$$

thus, a simple conditional Bernoulli model.

In Figure 3, we have shown the relations between the SORE model and its generalizations or restrictions. In Table III, general expressions are given for $E(Y|X,Z)$ in the six models of Figure 3, together with the correspondences with the logistic parametrization. It can be seen from Figure 3 that, starting from the saturated model, other models of $E(Y|X,Z)$ are obtained by applying successive restrictions. The saturated model is called M4 because it is specified by 4 parameters. In a similar way, the SORE model is called M3a because it is one of the models that can be specified by 3 parameters, another one being the logistic model without interaction, called here M3b. The six models of Figure 3 and the way they are obtained by restriction of another model can be considered as a planar directed graph.

Figure 3, Table III

3.3 Several Doses

In many studies, several doses of the same drug, namely $(a_1 \dots a_p)$ are on trial together with a placebo. In the framework of Section 3.1, we have to redefine the relation between the dose and the pharmacological (resp. the toxic) effects. Thus, we have to give new definitions of $E(\theta|X)$ and $E(\nu|X)$.

Two strategies can be used. A first one is to consider X as a numerical variable and to look for a function $f(X)$ for $X \in \mathbb{R}_+$ with a range in $[0,1]$ and that vanishes at the origin. A simple monotonic example could be:

$$f(X) = k[1 - \exp(-rX)] \tag{3.3.1}$$

where $k \in [0, 1]$ and $r \in \mathbb{R}_+$. A non-monotonic version could be:

$$f(X) = k[1 - \exp(-rg(X)] \tag{3.3.2}$$

where $g(\cdot)$ is such that $g(0) = 0$ but otherwise arbitrary.

Alternatively, in the spirit of a non-parametric strategy, one may consider a disjunctive coding of the doses i.e. $X = [X_0 \dots X_p]$ where X_0 stands for the control group and X_j for the drug at the dose a_j. We may then specify the relation with dose as follows:

$$f(X) = \sum_{0 \leq i \leq p} b_i X_i \tag{3.3.3}$$

with $b_i \in [0, 1]$.

4 Attributable effects

The introduction of the latent events $(\lambda, \theta, \mu, \nu)$ provides the SORE model with the possibility of distinguishing between latent and manifest treatment effects. This distinction is made in turn for therapeutic and for adverse effects. Essentially, the manifest effect of drug is obtained by comparing the expected effects in the drug-treated group $(X = 1)$ and in the control group $(X = 0)$. In this section, we try to build a bridge between the terminology of the SORE model and standard epidemiological concepts.

4.1 Attribution of therapeutic effects

Health improvement may result from the pharmacological action of the drug (λ). Thus, the Drug Attributable Therapeutic Effect (DATE) may be defined and is specified in the SORE model as:

$$\text{DATE} = E(\lambda|X = 1) - E(\lambda|X = 0) = \alpha - 0 = \alpha \tag{4.1.1}$$

The improvement may also result from a placebo effect (θ). Thus, the Placebo Attributable Therapeutic Effect (PATE) may be defined and is specified in the SORE model as:

$$\text{PATE} = E(\theta|X=1) - E(\theta|X=0) = \beta - \beta = 0 \tag{4.1.2}$$

Thus, the SORE model ensures the nullity of PATE, a desirable feature.
Finally, the Manifest Attributable Therapeutic Effect (MATE) will be defined and is specified in the SORE model as follows:

$$MATE = E(Z|X=1) - E(Z|X=0) = \alpha + \beta - \alpha\beta - \beta = \alpha(1-\beta) \tag{4.1.3}$$

Ignoring the SORE model (i.e. the fact that λ is latent) induces one to evaluate DATE by MATE i.e. introducing a bias by evaluating a property of the drug at the clinical level only. Thus, we may define and specify a Clinical Bias of Therapeutic Effect (CBTE) as follows:

$$CBTE = MATE - DATE = -\alpha\beta \tag{4.1.4}$$

Thus, DATE is systematically underestimated in clinical trials. Before controlled trials were used, DATE was evaluated by $E(Z|X=1) = \alpha + \beta(1-\alpha)$, which is clearly an overestimate unless $\alpha = 1$ or $\beta = 0$. The correction brought by the control group is thus an overcorrection for the therapeutic effect of placebo.

Suppose now that MATE has been evaluated but that the investigators realize that what they are really looking for is DATE. It is possible to correct MATE by dividing it by the probability of no therapeutic effect in the control group. If we call "Attributable Fraction of Therapeutic Effect" the fraction obtained, we see that:

$$AFTE = MATE/(1 - E(Z|X=0)) = \alpha(1-\beta)/(1-\beta) = \alpha = DATE \tag{4.1.5}$$

It is interesting to look at the way this problem was considered historically in epidemiology. Our definitions of MATE and AFTE correspond respectively to Berkson's index (Berkson 1958) and Sheps' excess risk or relative difference (Sheps 1961). A measure of "the relative value of a new treatment" similar to AFTE is given by Fleiss (1981).

4.2 Attribution of adverse effects

The analysis of side effects is somewhat more involved than the analysis of therapeutic effects. Let us indeed define the Drug Attributable Side Effect (DASE) and look at its specification in the SORE model :

$$DASE = E(\nu|X=1) - E(\nu|X=0) = \phi - 0 = \phi \tag{4.2.1}$$

Side effects may also result from nocebo action (μ). Thus, we define the Nocebo Attributable Side Effect (NASE) as follows:

$$NASE = E(\mu|X=1) - E(\mu|X=0) \tag{4.2.2}$$

Let us decompose NASE with respect to Z:

$$\begin{aligned} E(\mu|X=1) &= E(\mu|Z=1,X=1)E(Z|X=1) \\ &\quad +E(\mu|Z=0,X=1)[1-E(Z|X=1)] \end{aligned} \tag{4.2.3}$$

$$\begin{aligned} E(\mu|X=0) &= E(\mu|Z=1,X=0)E(Z|X=0) \\ &\quad +E(\mu|Z=0,X=0)[1-E(Z|X=0)]; \end{aligned} \tag{4.2.4}$$

substituting (4.2.3) and (4.2.4) into (4.2.2), we get:

$$NASE = \alpha(1-\beta)(\eta - \xi) \tag{4.2.5}$$

Finally, the Manifest Attributable Side Effect (MASE) is given by:

$$MASE = E(Y|X=1) - E(Y|X=0) \tag{4.2.6}$$

Or, by applying (3.1.1),(3.1.2),(3.1.3) and (3.1.4):

$$\begin{aligned} MASE &= (\alpha+\beta-\alpha\beta)(\phi+\eta-\phi\eta) \\ &\quad +(1-\alpha)(1-\beta)(\phi+\xi-\phi\xi) - \beta\eta - (1-\beta)\xi \end{aligned} \tag{4.2.6bis}$$

Re-arranging the terms, we get:

$$MASE = \alpha(1-\beta)(\eta-\xi) + \phi[(1-\xi) - (\alpha+\beta-\alpha\beta)(\eta-\xi)]$$
$$= NASE + DASE[(1-\xi) + (\alpha+\beta-\alpha\beta)(\eta-\xi)] \quad (4.2.6ter)$$

As before, if we ignore the SORE model, we are tempted to use MASE to evaluate DASE, introducing a Clinical Bias of Side Effect (CBSE) as follows:

$$CBSE = MASE - DASE = \alpha(1-\beta)(1-\phi)(\eta-\xi) - \phi[\xi + (1-\xi)\beta] \quad (4.2.7)$$

The relation between CBSE and α is linear, the slope of which is given by:

$$\frac{\partial CBSE}{\partial \alpha} = (1-\beta)(1-\phi)(\eta-\xi) \quad (4.2.8)$$

Thus, the magnitude of CBSE increases with α and this increase is directly proportional to the increase of the probability of side effects after improvement of the patient's status $(\eta-\xi)$. The increase in CBSE with α is also proportional to the probabilities of no placebo effect $1-\beta$ and to the probability of no pharmacological toxic effect of the drug $1-\phi$.

As we did for therapeutic effects, we look now to a transformation that could be applied to MASE to obtain DASE. The Attributable Fraction of Side Effects (AFSE) is defined separately for the improved $(Z=1)$ and unimproved $(Z=0)$ groups, namely:

$$AFSE(Z) = \frac{E(Y|X=1,Z) - E(Y|X=0,Z)}{1 - E(Y|X=0,Z)} \quad (4.2.9)$$

Eventually we get:

$$AFSE = E[AFSE(Z)] = E(Z)AFSE(Z=1) + (1-E(Z))AFSE(Z=0) \quad (4.2.10)$$

Our AFSE is thus the mean of two fractions. The properties of the SORE model imply that:

$$AFSE(Z=1) = AFSE(Z=0) = \phi \quad (4.2.11)$$

and therefore:

$$AFSE = \phi = DASE \tag{4.2.12}$$

A corrected expression for DASE can thus be obtained in the same way as a correct expression for DATE was obtained in (4.1.8).

A particular situation arises when $\eta = \xi$. In such a situation, side effects have only two possible causes: placebo toxicity ($\eta = \xi$) and drug toxicity (ϕ). It can be seen that $CBSE = -\eta\phi$, and that $MASE = \phi(1 - \eta)$. Finally, if $\eta = \xi = 0$, no side effects are observed in control patients, and all the side effects are caused by the drug.

4.3 A numerical illustration

We conclude this section by a numerical exercise in order to evaluate the order of magnitude of the different effects defined above. In Table IV, we give the CBSE for $\phi = \xi = \beta = 0.1$ and α varying from 0.5 to 0.9. It can be seen that for $\alpha = 0.9$ and $\beta = 0.1$, which amounts to an improvement rate of 91% in drug-treated patients, the CBSE can be considerable. Suppose that $\beta = \phi = \xi = 0.1$, $\alpha = 0.9$ and $\eta = 0.4$. We get :

$E(Z\|X = 1) = 0.91$	$MASE = 0.306$	$MATE = 0.81$
$E(Z\|X = 0) = 0.10$	$DASE = 0.10$	$DATE = 0.90$
$E(Y\|X = 1) = 0.436$	$NASE = 0.243$	$PATE = 0$
$E(Y\|X = 0) = 0.13$	$CBSE = 0.206$	$CBTE = -0.09$

In this example, a new drug achieves an improvement rate of 91% compared to 10% for the placebo, raising thus some hope for a better management of the disease. The rate of side effects, however, is disturbingly high: 43.6% versus 13% for the placebo. Before we look for another drug, we should keep in mind the possibility that a part of this 30% difference (here: the two thirds) is actually linked to the achievement of our therapeutic aim and is thus likely to be found again for all other effective drugs.

Table IV

A similar reasoning holds for cases with $\eta < \xi$ (i.e. the improvement in health decreases the risk of side effects). Suppose that $\beta = \phi = \eta = 0.1$, $\alpha = 0.9$ and $\xi = 0.4$. We get $CBSE = -0.276$ because the classical estimate for MASE is -0.176 instead of $+0.100$ for DASE. In such a case we are tempted to attribute protective effects to a drug that actually increases the probability of side effects. Another drug with similar curative properties would clearly be a better choice.

5 A Case Study

In a double blind randomized control trial, the drug DR was compared to a placebo for the relief of disease DI. Drugs belonging to the same therapeutic class as DR often exhibit the typical side effect SE so that this property can be anticipated from DR too. In this study, 312 patients were treated by DR and 103 were allocated to a control group. There was no clear-cut definition of improvement but, for each patient, an "improvement score" was computed, with values varying in the range from -100 to $+100$. We considered after discussion with clinical investigators that a score of at least $+50$ could be taken as defining improvement. Three different doses of DR were used (5 mg, 10 mg and 20 mg/day). The results are summarized in Table V.

Table V

If we pool the results obtained with all three doses of DR, it can be observed that SE occurs in 58 patients out of 312 (the estimate of $E(Y|X = 1)$ is thus 18.6%) versus 6 patients out of 103 in the control group (the estimate of $E(Y|X = 0)$ is thus 5.8%). Thus, the estimate of MASE is 0.128. The estimate of AFSE is 0.1347.

Moreover, SE was observed to occur in 43 of the 237 improved patients ($= 18\%$) and in 21 of the 178 non-improved patients ($= 11,8\%$), raising the question of the respective influences of the drug and of improvement. Estimates for α and β were respectively 0.28 and 0.45. We observe that $MATE = 0.154$ so that the clinical bias CBTE is -0.126.

In Table VI, we give a hierarchy of six models that can be defined by generalization or restriction of the SORE model. For each model, the m.l. estimates of the parameters and the maximized conditional log-likelihood were computed. The likelihood ratio statistic for the eight restrictions of Figure 3 is shown in Table VII. Models 3a and 3b show no significant difference of the quality of the fit. Since the likelihood ratio test does not show a significant difference between Model 3a and Model 2a, we are led to accept Model 2a as a satisfactory formalization of our trial (Atkinson 1970). Thus, there is a clear effect of the drug on the probability of side effects, and this probability is not significantly modified by the occurrence or lack of clinical improvement. The extent of the clinical bias CBSE depends on whether Model 3a or 2a is selected: we observe indeed that $CBSE = 0.003$ for M3a and that $CBSE = -0.008$ for M2a. Our estimate of AFSE is an overestimate for M3a.

Tables VI and VII

To take into account the doses of the active drug, a modified version of the SORE model was used, as described in Section 3.3. A hierarchy of models can be constructed as shown in Figure 4. At one of the top of the hierarchy, we find model SM4 (SORE model with 4 parameters). At the other top, we find model LM4 (logistic model with 4 parameters). By stepwise deconstruction of each of these models, we converge to the simple Bernoulli model M1 already shown in Table VI. All the models for several doses, together with the log likelihood for our data are given in Table VII. The likelihood ratio test for the restrictions of these models to null hypotheses are given in Table VIII.

Figure 4, Tables VIII and IX

The log likelihood of SM4 is -168.638, indicating a significant ($p = 0.0057$) improvement on the model without doses. To test the null hypothesis $\eta = \xi$, we fit the simpler model:

$$E(Y|X, Z) = k[1 - e^{-rX}](1 - \eta) + \eta$$

This time, the p-value is 0.489 (see Table VIII), and the null hypothesis cannot be rejected.

Finally, our SORE model includes only 4 parameters: k, r, η.

The logistic model can also be modified to accommodate several doses, as shown in Figure 4 and in Table VII. This time again, there is little ground for selecting the logistic rather than the SORE model or vice-versa. The observed data, together with the fitted values, are shown in Figure 5.

Figure 5

6 Conclusion

Adverse events will continue to be a source of problems in the analysis of clinical trials results. In this study, a special aspect of the problem has been investigated: the distinction between adverse events directly attributable to the drug (DASE) and adverse events where the drug acts only through its effect of health improvement (NASE). It is well-established conventional wisdom that drug-treated patients are usually more likely to exhibit adverse events than placebo-treated patients (i.e. MASE is positive). The regular occurrence of specific adverse reactions to some drugs can even be a problem for blindness maintenance throughout a trial.

SORE model has been shown to be flexible enough to handle this class of issues.

In this study, the case of continuous or "survival" health outcomes was not considered and should deserve special attention. Another lack of generality is that it includes many postulates of independence. It should perhaps be profitable to consider also, for example, cases where the placebo and pharmacological effects are not independent. For long trials, time should also be included in the model and precedence relations between effects should be taken into account. But, all in all, the approach of SORE modelling seems to offer a promising avenue for accomodating such extensions.

Nevertheless, we hope that this model, crude as it is, will allow to settle some problems related to the attribution of adverse events, a problem of considerable actuality since powerful but dangerous drugs are already widely available or under development and since toxicity is the most usual limit to therapeutic effectiveness. Moreover, the idea of SORE (integrating deterministic outcomes into a probabilistic model) could have applications in completely different fields.

Appendix

These maximum likelihood estimators have been obtained with the help of symbolic manipulations realized through the package MAPLE.

$$\hat{\beta} = \frac{N[011] + N[010]}{N[000] + N[001] + N[010] + N[011]}$$

$$\hat{\alpha} = \frac{(N[001] + N[000])(N[111] + N[110]) - (N[101] + N[100])(N[011] + N[010])}{(N[001] + N[000])(N[100] + N[101] + N[110] + N[111])}$$

Note that the m.l.e of $\beta = E(\theta)$ is equal to the proportion of patients improved in the control group. From Figure 2, this may also be viewed as a moment estimator of $\beta = E(Z|X = 0)$. Similarly, from (4.1.5) (i.e. $\alpha = AFTE$), the m.l.e of α may also be obtained as a moment estimator of

$$\alpha = [E(Z|X = 1) - E(Z|X = 0)]/[1 - E(Z|X = 0)].$$

It is readily seen that this estimator is always smaller than 1 and will be positive as soon as, in the maximum likelihhod estimation, $\hat{\xi} \geq \hat{\beta}$; this is restriction (3.2.6) satisfied by the sample.

$$\hat{\xi} = W$$

$$\hat{\eta} = \frac{W(aW^2 + bW + c)}{(dW - N[001])(eW - N[001])}$$

$$\hat{\phi} = \frac{W[(N[101] + N[100] + N[001] + N[000])W - (N[101] + N[001])]}{(W - 1)[(N[101] + N[100] + N[001] + N[000])W - N[001])}$$

where:

$$a = N[001](2N[000] + N[100] + N[101] - N[001] - N[110]) + N[000](N[101]$$
$$+N[100] + N[000] - N[110]) - N[110](N[100] + N[101])$$

$$b = N[001](-2N[000] + N[110] - N[100] - 2N[101] - N[111])$$
$$-N[000](N[101] + N[111]) + N[101]N[110] - N[100]N[111]$$

$c = N[001](N[101] + N[111] + N[001])$

$d = N[001] + N[000] + N[100]$

$e = N[001] - N[111] - N[110] + N[000]$

and W is a root satisfying :

$0 \leq \xi 1 \leq$

$0 \leq \eta \leq 1$

$0 \leq \phi \leq 1$

of the equation:

$$sW^3 + tW^2 + uW + v = 0$$

with:

$s = N^2[001]N[010] + 3N^2[001]N[000] + N[001]N[101]N[011]$

$+2N[001]N[010]N[000] + 2N[001]N[101]N[000] + 2N[001]N[100]N[000]$

$+N^2[001]N[011] + 3N[001]N^2[000] + N^2[001]N[100] + N^2[001]N[101]$

$+N[001]N[101]N[010] + N[001]N[100]N[011] + N[001]N[100]N[010]$

$+2N[001]N[011]N[000] - 2N[001]N[000]N[110] - N[001]N[110]N[101]$

$-N[001]N[110]N[100] - N[001]N[010]N[110] - 2N^2[001]N[110]$

$-N[001]N[110]N[100] - N[001]N[010]N[110] - N[001]N[011]N[110]$

$-N[000]N[100]N[110] + N^3[000] + N^2[000]N[100] + N^2[000]N[010]$

$+N^2[000]N[011] + N^2[000]N[101] + N^2[000]N[110] - N[010]N[100]N[110]$

$+N[011]N[000]N[100] - N[010]N[000]N[110] - N[011]N[000]N[110]$

$-N[011]N[100]N[110] - N[011]N[101]N[110] + N[010]N[100]N[000]$

$+N[011]N[101]N[000] - N[000]N[110]N[101] - N[010]N[110]N[101]$

$+N[010]N[101]N[000] + N^3[001]$

$$t = -2N^2[001]N[010] - 6N^2[001]N[000] - 2N[001]N[101]N[011] - 2N[001]$$

$$N[010]N[000] - 4N[001]N[101]N[000] - 2N[001]N[100]N[000]$$

$$-3N^2[001]N[011] - 3N[001]N^2[000] - 2N^2[001]N[100] - 3N^2[001]N[101]$$

$$-2N[001]N[101]N[010] - 2N[001]N[100]N[011] - N[001]N[100]N[010]$$

$$-4N[001]N[011]N[000] - N^2[001]N[111] + 2N[001]N[000]N[110]$$

$$+2N[001]N[110]N[101] + N[001]N[110]N[100] + N[001]N[010]N[110]$$

$$+2N^2[001]N[110] + 2N[001]N[011]N[110] - 2N[001]N[000]N[111]$$

$$-N[001]N[111]N[100] - N[001]N[010]N[111] - N[111]N^2[000]$$

$$-N[011]N^2[000] - N101N^2[000] - N[011]N[000]N[100]$$

$$+N[011]N[000]N[110] + N[011]N[100]N[110] + N[011]N[101]N[110]$$

$$-N[011]N[101]N[000] + N[000]N[110]N[101] + N[010]N[110]N[101]$$

$$-N[010]N[111]N[000] - 3N^2[001] - N[010]N[111]N[000]$$

$$-N[010]N[111]N[100] - N[111]N[000]N[100]$$

$$u = N[001](3N^2[001] + N[001]N[010] + 3N[001]N[000] + N[001]N[100]$$

$$-N[001]N[110] + 3N[001]N[011] + 3N[001]N[101] + 2N[001]N[111]$$

$$N[011]N[110] + N[010]N[111] + 2N[011]N[000] + 2N[000]N[111]$$

$$+N[101]N[011] + N[101]N[010] + N[100]N[011] + N[111]N[100]-$$

$$N[110]N[101] + 2N[101]N[000])$$

$$v = -N^2[001](N[001] + N[111] + N[011] + N[101])$$

The multiple solutions correspond to restrictions (3.2.9) and (3.2.10). Note that the m.l.e estimators of (η, ξ, ϕ) are not obtained as simple moment estimators because, as can be seen from Figure 3, these parameters are not variation-free in view of the restriction (3.2.10), whereas α and β are variation-free. The separation between the estimation of (α, β) and of (η, ξ, ϕ) is substantiated in the block

diagonal structure of the information matrix, given below:

$$E\begin{pmatrix} I_{\alpha\alpha} & I_{\alpha\beta} & 0 & 0 & 0 \\ I_{\alpha\beta} & I_{\beta\beta} & 0 & 0 & 0 \\ 0 & 0 & I_{\phi\phi} & I_{\phi\eta} & I_{\phi\xi} \\ 0 & 0 & I_{\phi\eta} & I_{\eta\eta} & 0 \\ 0 & 0 & I_{\phi\xi} & 0 & I_{\xi\xi} \end{pmatrix}$$

where:

$$I_{\alpha\alpha} = \frac{N[100]+N[101]}{(1-\alpha)^2} + \frac{(1-\beta)(N[110]+N[111])}{(\alpha+\beta-\alpha\beta)^2}$$

$$I_{\alpha\beta} = \frac{(N[110]+N[111])}{(\alpha+\beta-\alpha\beta)} + \frac{(1-\alpha)(1-\beta)N[111]}{(\alpha+\beta-\alpha\beta)^2}$$

$$I_{\beta\beta} = \frac{N[010]+N[011]}{\beta^2} + \frac{N[000]+N[001]+N[100]+N[101]}{(1-\beta)^2} + \frac{(1-\alpha)^2(N[110]+N[111])}{(\alpha+\beta-\alpha\beta)^2}$$

$$I_{\phi\phi} = \frac{(1-\xi)^2 N[101]}{(\phi+\xi-\phi\xi)^2} + \frac{}{(}1-\eta)^2 N[111](\phi+\eta-\phi\eta)^2 + \frac{N[100]+N[110]}{(1-\phi)^2}$$

$$I_{\phi\eta} = \frac{N[111]}{(\phi+\eta-\phi\eta)} + \frac{(1-\phi)(1-\eta)N[111]}{(\phi+\eta-\phi\eta)^2}$$

$$I_{\phi\xi} = \frac{N[101]}{(\phi+\xi-\phi\xi)} + \frac{(1-\phi)(1-\xi)N[101]}{(\phi+\xi-\phi\xi)^2}$$

$$I_{\eta\eta} = \frac{N[011]}{\eta^2} + \frac{N[010]+N[110]}{(1-\eta)^2} + \frac{(1-\phi)^2 N[111]}{(\phi+\eta-\phi\eta)^2}$$

$$I_{\xi\xi} = \frac{N[001]}{\xi^2} + \frac{N[000]+N[100]}{(1-\xi)^2} + \frac{(1-\phi)^2 N[101]}{(\phi+\xi-\phi\xi)^2}$$

TABLE I

Parametrization of a SORE model

Distribution	Structural zeroes	Independence Restrictions	Parameters
X	0	0	Q
$\theta \vert X$	0	1	β
$\lambda \vert \theta, X$	2	1	α
$Z \vert \lambda, \theta, X$	8	0	-
$\mu \vert Z, \lambda, \theta, X$	10	4	η, ξ
$\nu \vert \mu, Z, \lambda, \theta, X$	24	7	ϕ
$Y \vert \nu, \mu, Z, \lambda, \theta, X$	64	0	-
127	108	13	6

TABLE II

Expectations of a random sampling generated by SORE

$$E(N[000]) = (1-\beta)(1-\xi)Qn$$

$$E(N[001]) = (1-\beta)\xi Qn$$

$$E(N[010]) = \beta(1-\eta)Qn$$

$$E(N[011]) = \beta\eta Qn$$

$$E(N[100]) = (1-\alpha)(1-\beta)(1-\phi)(1-\xi)(1-Q)n$$

$$E(N[101]) = (1-\alpha)(1-\beta)(\phi+\xi-\xi\phi)(1-Q)n$$

$$E(N[110]) = (\alpha+\beta-\alpha\beta)(1-\phi)(1-\eta)(1-Q)n$$

$$E(N[111]) = (\alpha+\beta-\alpha\beta)(\phi+\eta-\phi\eta)(1-Q)n$$

TABLE III

A family of six models generated from the saturated model by a succession of restrictions.

MODEL	$E(Y\|X,Z)$
M4 (saturated)	$\kappa^{XZ}\gamma^{(1-Z)X}\eta^{Z(1-X)}\xi^{(1-Z)(1-X)} = \frac{e^{a+bX+cZ+dXZ}}{1+e^{a+bX+cZ+dXZ}}$
M3a (SORE)	$(\phi+\eta-\phi\eta)^{XZ}(\phi+\xi-\phi\xi)^{(1-Z)Z}\eta^{Z(1-X)}\xi^{(1-Z)(1-X)}$
M3b (logistic without interaction)	$\frac{e^{a+bX+cZ}}{1+e^{a+bX+cZ}}$
M2a	$(\phi+\eta-\phi\eta)^{X}\eta^{(1-X)} = \frac{e^{a+bX}}{1+e^{a+bX}}$
M2b	$\eta^{Z}\xi^{(1-Z)} = \frac{e^{a+cZ}}{1+e^{a+cZ}}$
M1	$\eta = \frac{e^{a}}{1+e^{a}}$

TABLE IV

Expected clinical activity attributable risk for some values of the parameters α and η and for the plane $\beta = \phi = \xi = 0.1$.

$CBSE$	$\eta = 0.1$	$\eta = 0.2$	$\eta = 0.3$	$\eta = 0.4$
$\alpha = 0.5$	-0.01	0.030	0.069	0.109
$\alpha = 0.6$	-0.01	0.038	0.085	0.133
$\alpha = 0.7$	-0.01	0.046	0.101	0.157
$\alpha = 0.8$	-0.01	0.054	0.118	0.181
$\alpha = 0.9$	-0.01	0.062	0.134	0.206

TABLE V

Observed results of the case study

	Improved		Not Improved	
	Adverse Effects	No Adverse Effects	Adverse Effects	No Adverse Effects
PLACEBO	2	45	4	52
DR				
5 mg	7	45	2	48
10 mg	18	53	6	29
20 mg	16	51	9	28
total drug	41	149	17	105

TABLE VI

The m.l. estimations of the parameters and the maximized conditional log-likelihood for six related stochastic models of the data.

MODEL	Free Parameters	Log-likelihood	Estimates
M4	$\kappa, \gamma, \eta, \xi$	-171.031	$\kappa = 0.2157$
saturated	or (a, b, c, d)		$\gamma = 0.1393$
			$\eta = 0.0425$
			$\xi = 0.0714$
M3a	ϕ, η, ξ	-172,451	$\phi = 0.124$
SORE			$\eta = 0.079$
			$\xi = 0.0514$
M3b	a, b, c	-171.724	$a = -2.984$
Conditional			$b = 0.4028$
Logistic			$c = 1.2504$
M2a	ϕ, η	-172.708	$\phi = 0.135$
	or (a, b)		$\eta = 0.058$
M2b	η, ξ	-176.826	$\eta = 0.181$
	or (a, c)		$\xi = 0.118$
M1	η	-178,431	$\eta = 0.154$
	or a		

TABLE VII

The m.l. estimators of the parameters and the maximized conditional log likelihood for six related stochastic models of the data.

H_1	H_0	Test statistic	p
$M4$	$M3a$	2.84	0.0919
$M4$	$M3b$	1.38	0.2401
$M3a$	$M2a$	0.51	0.4751
$M3a$	$M2b$	8.75	0.0031
$M3b$	$M2a$	1.97	0.1604
$M3b$	$M2b$	10.2	0.0014
$M2a$	$M1$	11.45	0.0007
$M2b$	$M1$	3.21	0.0732

TABLE VIII

The hierarchy of models for several doses.

Model	$E(Y\|X,Z)$	Log-likelihood	Estimates
LM4	$\frac{e^{\beta_0+\beta_1 Z+\beta_2 X+\beta_3 XZ}}{1+e^{\beta_0+\beta_1 Z+\beta_2 X+\beta_3 XZ}}$	-169.2815	$\beta_0 = 2.8146$
			$\beta_1 = -0.6449$
			$\beta_2 = -0.0860$
			$\beta_3 = 0.0245$
SM4	$K[1-e^{rX}](1-\eta)^Z(1-\xi)^{1-Z}$ $+\eta^Z\xi^{1-Z}$	-168.638	$\eta = 0.071734$
			$\xi = 0.046317$
			$\kappa = 0.347614$
			$r = -0.0441$
LM3	$\frac{e^{\beta_0+\beta_1 Z+\beta_2 X}}{1+e^{\beta_0+\beta_1 Z+\beta_2 X}}$	-169.484	$\beta_0 = 2.6483$
			$\beta_1 = -0.3689$
			$\beta_2 = -0.0706$
SM3	$k[1-e^{rX}](1-\eta)+\eta$	-168.877	$\eta = 0.052989$
			$\kappa = 0.31275$
			$r = -0.056909$
M2b	$\eta^Z\xi^{(1-Z)} = \frac{e^{\beta_0+\beta_1 Z}}{1+e^{\beta_0+\beta_1 Z}}$	-176.826	$\eta = 0.181; \beta_0 = 2.0117$
			$\xi = 0.1179; \beta_1 = -0.505$
LM2a	$\frac{e^{\beta_0+\beta_2 X}}{1+e^{\beta_0+\beta_2 X}}$	-170.29	$\beta_0 = 2.449$
			$\beta_1 = -0.0734$
M1	η	-178.431	$\eta = 0.18$

TABLE IX

Restrictions to null hypotheses tested by the likelihood ratio statistic and the chi squared distribution.

H1	H0	LR statistic	degr. freedom	p
SM4	SM3	0.478	1	0.489
SM4	M2b	16.376	2	0.00028
LM4	LM3	0.405	1	0,524
LM3	M2b	14.684	1	0.00013
LM3	LM2a	1.62	1	0.203
SM3	M1	19.108	2	0.00007
M2b	M1	3.21	1	0.073
LM2a	M1	16.282	1	0.00005

Figure 1

The graph of possible trajectories in SORE

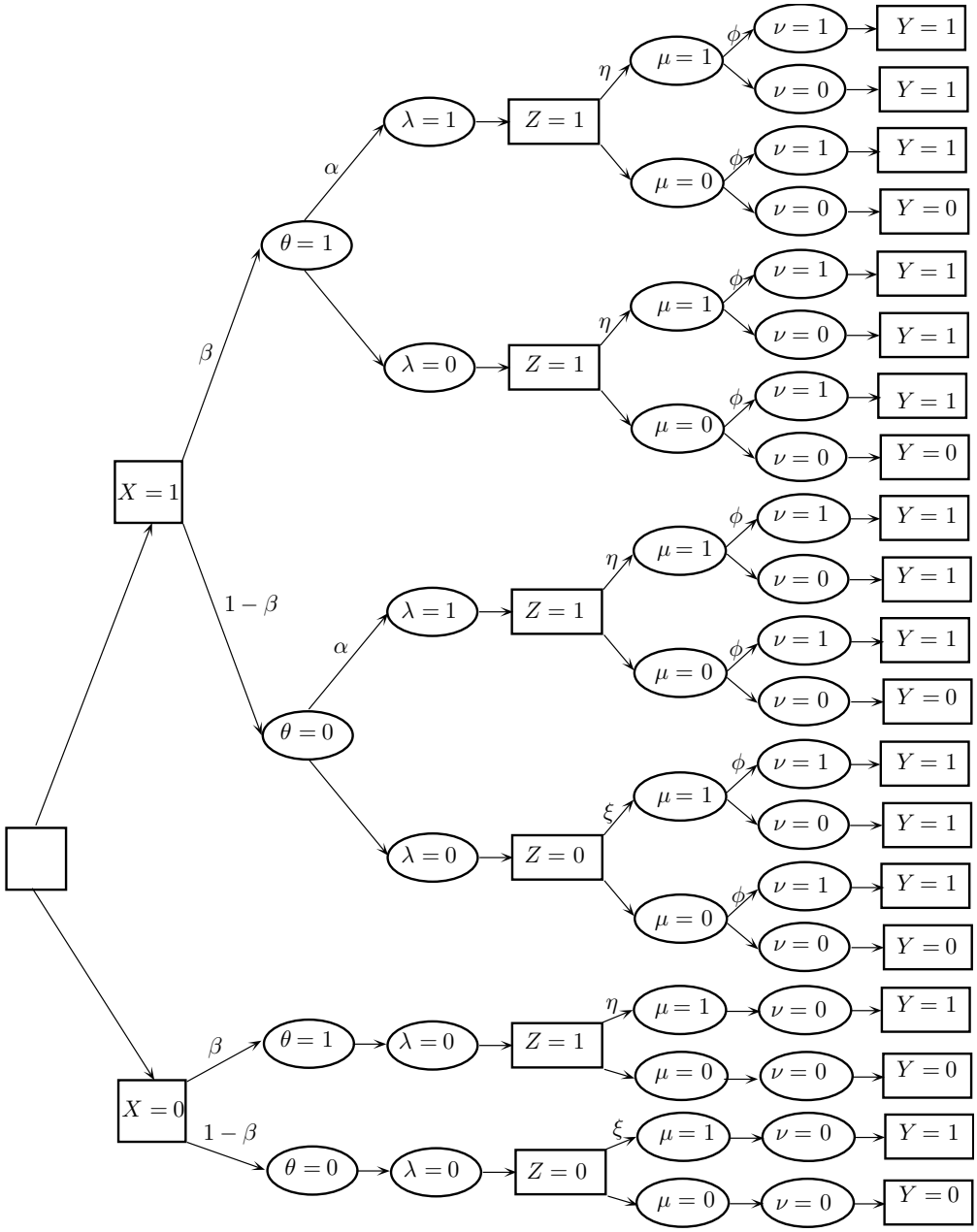


Figure 2

Trajectories in the space of observables

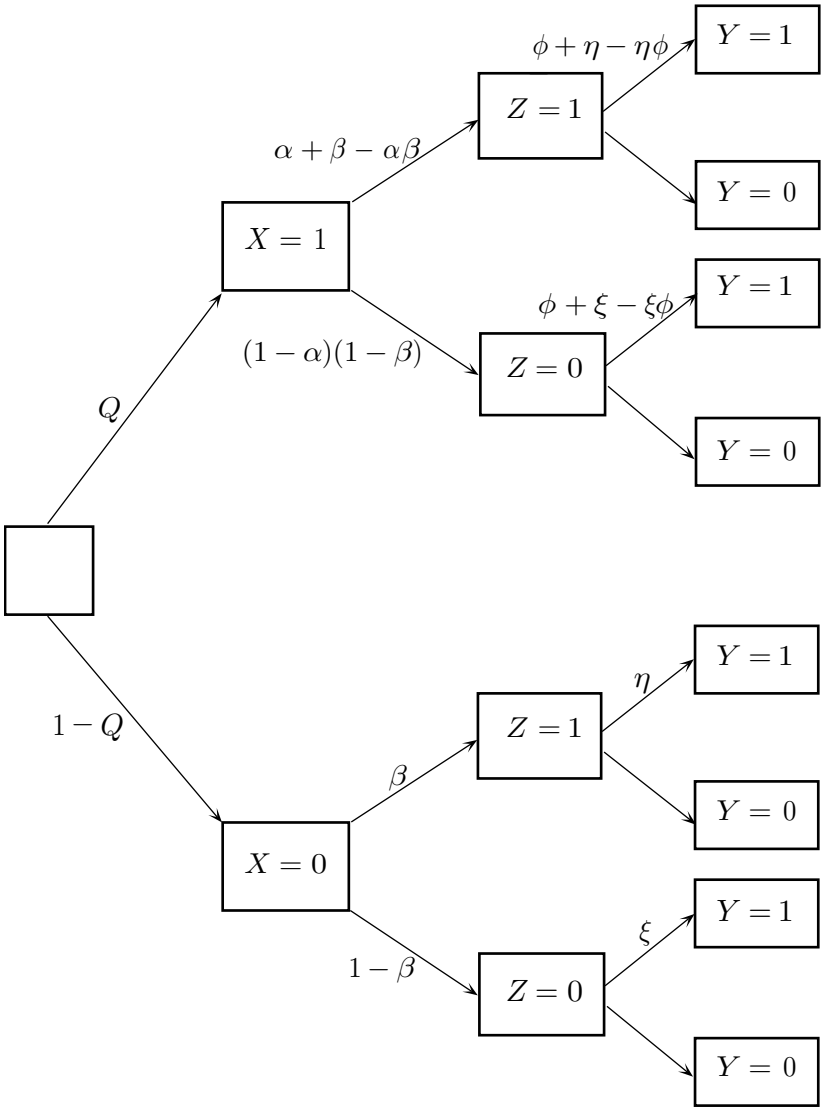
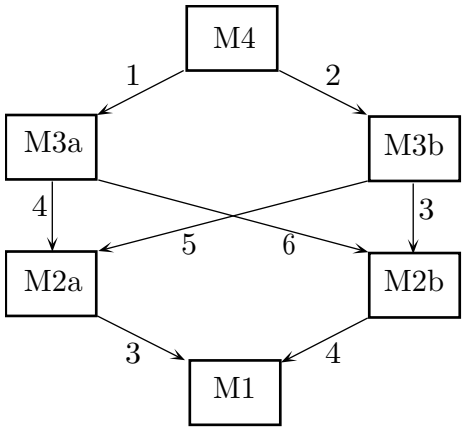


Figure 3

Interrelations between six models



Models:

M4 = saturated

M3a: SORE

M3b: logistic without interaction

M2a: no effect of improvement

M2b: no effect of the drug

M1: no effect of any covariable

Restrictions

1: $(1-\eta)/(1-\xi) = (\kappa-\eta)/(\gamma-\xi)$ (3.2.10)

2: $(1-\eta)/(1-\xi) = ((1-\kappa)/\kappa)(\gamma/(1-\gamma))(\eta/\xi)$ (3.2.14) or $d = 0$ (3.2.13)

3: $\phi = 0$

4: $\eta = \xi$

5: $\kappa = \gamma$ or $c = 0$

6: $\gamma = \xi$ or $\beta = 0$

Figure 4

Hierarchy of models for several doses

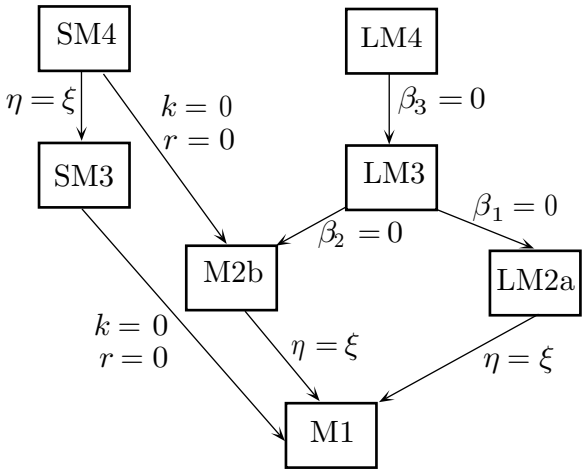
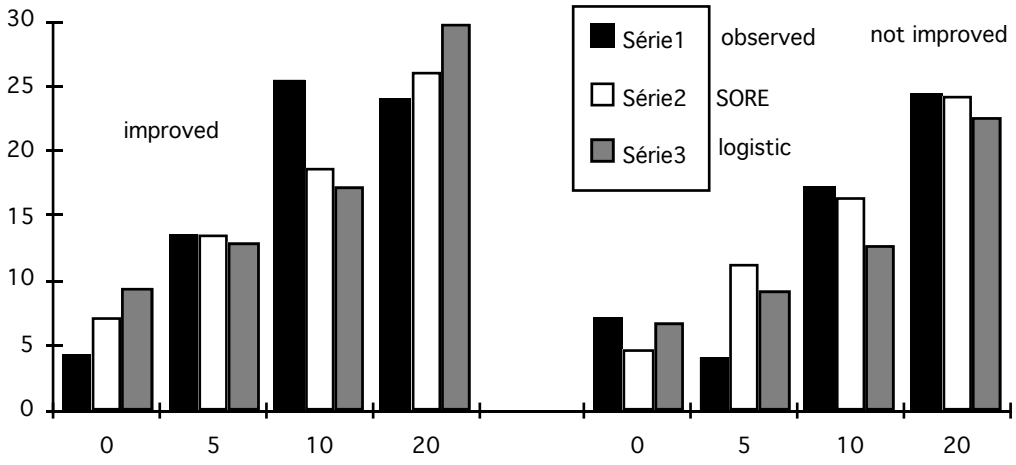


Figure 5

Observed and fitted values of the case study



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