# Analysis of a study of rheumatoid arthritis by the potential outcomes framework

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**Abstract**

The advantages of the potential outcomes framework, a particular application of multiple imputation, over adjustment for confounders by ordinary regression are demonstrated on the ARQUALIS study of patients sufferring from rheumatoid arthritis.

**Keywords:** Multiple imputation; potential outcomes; treatment-selection process.

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## 1. Introduction

Although randomisation is a key principle in experimental design, it cannot always be implemented in studies of medical interventions, leaving an important role for observational studies in epidemiology, especially in studies of chronic diseases which do not have a clinical treatment that might be observed over a short period of time. Randomised studies tend to have a very strict protocol, but are relatively easy to analyse, with principal difficulty arising from their imperfect implementation (incorrect regimen, drop-outs, and the like). In contrast, the protocol of a typical observational study is much less demanding, but its analysis has to address the issue of non-ignorable assignment of subjects to treatments.

Alternative treatments can be compared by regression analysis, in which adjustment is made for confounders. Satisfying its assumptions, normality and linearity, e.g., by suitable transformations, is a non-trivial task. One assumption is rarely satisfied — that treatment effect is constant. Without it, interpretation of the results is often impossible. In the potential outcomes framework, these problems are sidestepped by considering subject-specific treatment effects, and estimating their average for a specific set of subjects.

The fundamental problem with potential outcomes, that we can observe the outcome for at most one of the alternative treatments, is addressed by forming pairs of subjects matched on their background variables; the subjects in a pair differ only in the treatment they received. When there are many background variables, this can be accomplished by propensity score analysis, which converts the problem of matching to a univariate task. In fact, it is wise to record as many background variables as is practicable, to improve the chances that they are sufficient for the description of the treatment-selection process; that is, conditional on them, the treatment assignment is at random.

With the matched pairs, the comparison is straightforward, by treating them as if they were assigned to treatments by a controlled design. The uncertainty in the formation of the pairs is addressed by forming replicate (plausible) sets of pairs, and combining the analyses of the sets by the established 'rules' for multiply completed datasets ([2] and [3]).

We applied the potential outcomes framework in the analysis of ARQUALIS, a multicentre study of the quality of life of patients with rheumatism arthritis (RA), conducted in medical institutions in Catalonia in 2004–2005. The presentation is based on [1], although it will also discuss some experiences with the method gained later.

## 2. Application

In one analysis, we pose the question whether overweight patients benefit less from the treatment of RA than normal-weight patients do. This can be phrased in the language of causal analysis as excess weight being the cause and lack of progress as the effect. Excess weight cannot be regarded as a cause because, in our context we do not contemplate manipulation of one's bodymass. However, the matching on background is very useful nevertheless, because it plays the role of adjustment, much more effectively than by regression.

We combine multiple imputation (MI) for two sources of incompleteness: nonresponse and potential outcomes, highlighting the universality of MI as a general tool for the analysis of observational studies. Whereas in regression the principal analytical effort is in model selection, in which the outcomes are intimately involved, with potential outcomes, the main effort is invested in the propensity scoring, finding a models for the treatment assignment which yields a balance of all the covariates in the matched pairs. The outcomes are not involved in this analysis, so the results cannot be subverted; the matching can be carried out between the collection of the background variables and the conclusion of the study. This feature has a flavour of an analysis of a clinical trial. Indeed, the purpose of the potential outcomes framework is to rescue as much as possible of the observational study for an analysis that would closely resemble the analysis of a randomised study.

Sensitivity analysis is a key element of the analysis proper. It entails reanalyses with altered settings of some of the parameters. For example, in the comparison of overweight and normal-weight patients,d we have to agree on the definition of these two categories (by the threshold values of the bodymass index). Thus the result of an analysis is not a single inferential statement, but an open-ended exploration of the plausible alternative conclusions. When the results are affected by the setting only slightly, we have an unequivocal conclusion.

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