Evidence, Eminence and Extrapolation

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A full independent drug development programme to demonstrate efficacy may not be ethical and/or feasible in small populations such as paediatrics populations or orphan indications. Different levels of extrapolation from a larger population to smaller target populations are widely used for supporting decisions in this situation. There are guidance documents in drug regulation, where a weakening of the statistical rigour for trials in the target population is mentioned to be an option for dealing with this problem. To this end we propose clinical trials designs, which make use of prior knowledge on efficacy for inference.

We formulate a framework based on prior beliefs in order to investigate when the significance level for the test of the primary endpoint in confirmatory trials can be relaxed (and thus the sample size can be reduced) in the target population while controlling a certain posterior belief in effectiveness after rejection of the null hypothesis in the corresponding confirmatory statistical test.

We show that point-priors may be used in the argumentation since under certain constraints they have favourable limiting properties among other types of priors.

The crucial quantity to be elicited is the prior belief in the possibility of extrapolation from a larger population to the target population. We try to illustrate an existing decision tree for extrapolation to paediatric populations within our framework.