DOSE ESCALATION TRIALS

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Several cohorts of healthy volunteers are recruited. The aim is to demonstrate safety of doses which are likely to be clinically active.

Terminology: Cohort is a group of subjects treated concurrently with dose in series of consecutive time periods [1].

Objective

To escalate doses up a predetermined series until a dose level or range of dose levels is identified that is suitable use in later trials. Doses chosen for further investigation are considered to be acceptable safe, certain cases therapeutic benefit is also considered.[3] Conventional Approach

For many compounds it is anticipated that adverse events will be few and phase I subjects will be healthy volunteers.

Methodology

The methodology constructed for studies involves the dose levels to be administered in successive periods. The choice for the doses to be administered are made to maximize some gain function, and the two possible choices that are of particular interest are patient gain and variance gain, see (Edler L 2001), O’Quigley (2001), Whitehead J.(2001), Rosenberger WF (2002), Zhou Y.

Regression Model for Bivariate Responses

The review of [5] is considered for the study. The dose levels in this trial are denoted by S_i; i = 1 . . . n. Successive periods (cohort) is denoted by (P_j); j = 1 . . . k. The active dose administered to S_i in P_j is denoted as d_{ij} for those combinations of i and j. Suppose that at the start of the study a number of doses d(1) < . . . <d(m) are available for administration to successive cohorts of dose levels.

Logistic Regression Model is used to model the binary response of occurrence of a DLE or not.

The Logistic Regression Model involves 2 parameters 1 and 2 and considers the probability of a dose limiting event. The procedure considers the decision on what doses to be recommended for the next cohort of subjects based on the prior or the current posterior the data observed so far and the selection criteria. The dose limiting event is considered to have a prior beta distribution. The posterior distribution is unimodal and the modal estimates of the parameters considered are robust. Posterior modal estimates are easy to obtain and can make simulations quicker than full Bayes estimates. Optimal and Safe Dose Escalation of the dose selection is based on the criteria to maximize the therapeutic effects and minimize side effects.

References


