Clinical Research of drugs for rare disease: Issues and open questions

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All new drugs must be studied through adequate and well-controlled studies to verify their safety and efficacy.

The design of all clinical trials must include a control such a placebo, dose comparison or other active treatment1.

Although these prerequisites apply to all drugs, Regulatory Authorities may wave them "in whole or in part" at their discretion in circumstances in which such trials are not possible or may not be scientifically justified.

The most common scenario in which this happen is the one for drugs intended for rare diseases2.

A growing number of studies have confirmed that orphan drugs are routinely approved in Europe and in the United States on the basis of data that are more limited than the ones on which approval decisions are made for drugs intended for non rare diseases3.

Two-thirds of orphan drugs have been approved on the basis of data not acceptable for other drugs4.

Differences in premarketing clinical studies are mainly related to the fact that orphan drugs can be tested only in small numbers of patients, given the limited patients population with the rare disease.

Alternatives to traditional randomized trials allow prospective evaluation of drugs for rare diseases, accounting for the small patient population and lack of comparators.

These alternatives include adaptive randomized designs, crossover studies and n-of-1 trials.

In particular adaptive designs have been touted as offering a particular opportunity for patients with rare diseases5, giving the difficulties Sponsor face in recruiting patients.

Crossover trials can be used when the disease of interest is chronic and stable and when the treatment under study is effective in symptom control but not cure the disease and has fast onset and a short-life.

N-of-1 studies are crossover trials in single patients and can be used in some specific situations with the great limit of their generalizability6.

Independently from all chosen design selected in the protocol design it is of fundamental importance to set up an efficient network and management in conducting such trials.

It is also of paramount importance to set up efficient strategies for post marketing analysis2.

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