Subgroup analysis: trying to get more from less?

Comment on 'Draft Guideline on the investigation of subgroups in confirmatory clinical trials' (EMA/539146/2013)

ABSTRACT

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The possibility that the effects of treatment vary from subgroup to subgroup is one that disturbs all who run clinical trials. The fear is that a treatment that seems to be beneficial on average may be of little benefit to some.

However, clinical trials are generally powered so as to be of adequate size to prove that a treatment works on average, that is to say on all patients studied. They are therefore not generally of adequate size to prove that they work for a subgroup of patients, still less of an adequate size to demonstrate that the effect of treatment is different from one subgroup to another.

Furthermore, the attempt to prove differential efficacy in subgroups is subject to two logical difficulties. First, there is a problem of an infinite regress. If one is not satisfied with the result that the drug works on average, why should one be satisfied with the result that it works on average in a given subgroup? What about the effect in subgroups of the subgroup? Secondly, there is always the problem of subgroup definition. Consider a genetic locus that is not itself causally involved in any modifying pathway but is fortuitously linked in the trial under consideration with one that is. Using this as a means of defining subgroups may be useless for future treatment.

However, one should not allow the best to become the enemy of the good. Having proven that a new treatment was on average highly beneficial it would be illogical for patients not to take it, because it had not been proven to be beneficial to all, but instead to prefer an old treatment now proven worse on average.

Thus, the appropriate attitude in using subgroup information is one of cautious conservatism. One should be prepared to use an approach of using treatments that are beneficial on average until convincing evidence that this average policy can be improved upon is provided.