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Enrichment Strategies

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FDA recently released draft guidance document, Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products that describes a number of ways clinical trials can select populations for study in which showing a drug effect, if one is present, will be more likely. In addition to helping trials succeed in their goals, enrichment strategies may help target treatments to the populations in which they will be most useful. The Agency is very interested in targeting treatments to specific patient populations, and in addition to this new guidance has over the years issued a number of guidances providing information about clinical trial designs and demonstrating effectiveness.

What is Enrichment? Clinical trials are not designed to demonstrate the effectiveness of a treatment in a random sample of the general population. Sponsors use a variety of strategies to select a population in which the effect of a drug, if there is one, can more readily be demonstrated. All of these selection strategies can be described as enrichment of the study population. This is not new, but the new guidance considers a broad range of ways to do this. Some of the selection strategies are obvious (e.g., patients are enrolled only if they have the disease that the drug being studied is intended to treat), but there are many more ways in which patients can be chosen to make detection of a treatment effect more likely.

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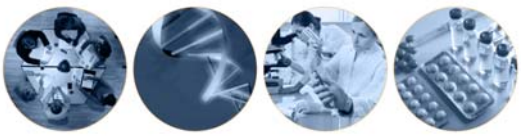
Enrichment Strategies fall into three broad categories:

- Strategies to decrease heterogeneity – These include selecting patients with baseline measurements (e.g. blood pressure, exercise ability, symptom score) that have low within patient variability) and excluding patients whose disease or symptoms improve spontaneously. The decreased variability provided by these strategies increases study power.

Example: Defining entry criteria carefully to ensure that entered patients actually have the disease that is being studied and training investigators to adhere to protocol-specified entry definitions and criteria; enrolling patients whose symptoms do not go away during a placebo lead-in period.

- Prognostic enrichment strategies – Selecting patients with a greater likelihood of having a disease-related endpoint event (for event-driven studies) or a substantial worsening in condition (for continuous measurement endpoints). These strategies will not alter relative effect, but will increase the absolute effect difference between groups.

Example: Early studies of effects of lipid-lowering drugs on cardiovascular outcomes enrolled patients with a recent heart attack and very high HDL cholesterol (i.e. people with a high risk of death or a heart attack).



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- Predictive enrichment strategies − Selecting patients more likely to respond to the drug treatment than other patients with the condition being treated. Such selection can lead to a larger effect size (both absolute and relative) and permit use of a smaller study population. Selection of patients could be based on a specific aspect of a patient's physiology or a disease characteristic that is related in some manner to the study drug's mechanism, or it could be empiric (e.g., the patient has previously appeared to respond to a drug in the same class).

Example: Proteomic markers, such as the HER 2/neu marker in breast cancer indicating potential for response to trastuzumab or tumor EGFR markers indicating potential response to drugs that act by inhibiting EGFR, and genetic markers that indicate ability to respond to a drug's mechanism of action can be used to identify potential responders, a rapidly growing enrichment strategy in oncology and also recently used to study drugs for cystic fibrosis and hepatitis C.

To Use or Not to Use? The decision to use an enrichment design is largely left to the sponsor of the investigation, but like the entire research and clinical communities, FDA is very interested in:

- Targeting treatments to the people who can benefit from them (i.e., individualization).

- The ability of the study to demonstrate effectiveness, which can be enhanced by using an enriched population.

- Describing study findings properly in drug labeling.

There are many reasons to use such designs, including an enhanced benefit–risk relationship in the enriched population if a population with an increased likelihood of response can be identified, and efficiency in drug development, as studies are more likely to succeed and may be smaller.

Two critical considerations when contemplating the use of enrichment designs include whether the enrichment strategy can be used to identify the patients to whom the drug should be given, and whether the drug might be useful in a broader population that was studied than would otherwise be necessary.

Well-controlled enrichment studies, if successful, provide clear evidence of effectiveness in the population studied. In many cases, however, questions will remain as to how to identify the patients to which the data apply and whether there is some effect, even if smaller, in the non-enriched patient population. This pattern is greatest when predictive enrichment is used and the guidance encourages study of at least some patients without the enrichment markers or with lower levels of it. FDA is prepared to approve drugs studied primarily or even solely in enriched populations and will seek to ensure truthful labeling that does not overstate either the likelihood of a response or the predictiveness of the enrichment factor. But the extent of data that should be available on the non-enriched subgroup should always be considered. Post-market commitments or requirements may be requested to better define the full extent of a drug's effect, including efficacy and safety studies and trials in a broader population.

Thank you once again for your attention. Look for our next issue in May…

Cheers,

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CDER Small Business Assistance

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