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Managed Access Program Synergies with Clinical Studies

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Managed access programs (MAPs), sometimes referred to as expanded access programs, named-patient programs, compassionate use programs, or patient or cohort programs, use country-specific regulatory mechanisms to enable the legal and ethical supply of experimental medicines to patients in need.[1,2]

In a previous article ("Supplementing Clinical Development with a Managed Access Program"), we discussed how MAPs can complement a clinical development program.[2] In this article, we take a closer look at three possible perceptions about MAPs and discuss how they are essentially unfounded:

- MAPs can compete with clinical studies for patients, slowing clinical development and delaying marketing approval.
- MAPs might generate negative safety or efficacy data that could derail clinical development and block marketing approval.
- MAPs can compete with clinical studies for scarce experimental medications.

Do MAPs compete with clinical studies for patients?

MAPs can be very attractive to patients, since patients are guaranteed to receive the active drug. In addition, treatment protocols are usually much less arduous than study protocols.

Nevertheless, both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) encourage biopharmas to give enrollment priority to clinical studies over MAPs. According to the EMA, "Patients should always be considered for inclusion in a clinical study before being offered programs outside the clinical study."[3] According to the FDA, this type of access is intended for patients who do not meet the clinical study enrollment eligibility criteria, live too far from study sites, or are not able to enroll for any other reason.[4] Also, some regulators will only allow early access when there is an active clinical trial or if the dossier is going through a marketing authorization.

In most cases, MAPs must meet the following criteria:

- The drug is intended to treat a serious or life-threatening disease or condition, based on the clinician's medical judgment.
- There are no comparable or satisfactory treatment alternatives available.
- The MAP will not interfere with ongoing clinical studies or development of the drug towards market approval.
- The presumed benefit to the patient outweighs the potential risk in the context of the disease or condition.
- Any adverse events or negative patient outcomes must be reported.
- Any research or commercial objectives must be secondary to the primary intent of treatment. However real-world data collected during a MAP can provide further insights to support regulatory submissions and/or health technology assessment dossiers and, at minimum, can be published.

Clinical studies typically have very narrow eligibility criteria and operate in only certain countries. Study sponsors can thus minimize enrollment conflicts by creating eligibility and geographical criteria for the MAP program that address the rest of the patient population,

including even other diseases. A MAP program can offset any potential conflicts by identifying patients that qualify for a study and referring those patients to a nearby research site.

What happens when a study participant concludes that he or she is in the placebo arm and drops out of the study to enroll in a MAP? In one reported case, the study sponsor refused the participant's request, since the change would go against MAP principles.[5]

Can MAPs generate negative safety data that derail clinical development and block marketing approval?

Patients excluded from clinical studies can be sicker than those participating in a clinical study. For example, they might be terminally ill, have co-morbidities, or have not responded positively to other therapies. These factors can increase their risk for negative outcomes. This patient population poses a potential problem, since the last thing a biopharma wants is any evidence that an experimental drug is unsafe or ineffective.

FDA regulations require the sponsor company conducting a MAP to report information on adverse events.[6] A clinical development program ensures that safety and efficacy are studied in a scientifically sound process. However, if even a single MAP participant has a serious adverse event, the news could be blown out of proportion by the biopharma's investors, the regulatory authorities, the media, or potential study participants.

To minimize this possibility, biopharmas can establish MAP eligibility criteria more in line with the anticipated labelled indication and expand these criteria over time as more about the drug becomes known.

It is, however, important to highlight that payers are interested in data that relates to a real-world population, so having MAP eligibility criteria broader than those of a clinical study should be considered.

The FDA is more likely to issue a clinical hold based on an adverse event report than to reject a drug based on that same report. The record shows very little evidence of clinical holds based on adverse events in a MAP:

> The FDA Center for Drug Evaluation and Research (CDER) published a study of regulatory actions recorded during the 10-year period from 2005 through 2014. They found that clinical holds relating to adverse events occurred in connection with 0.2% of patients receiving treatment under expanded access, compared to 7.9% for all commercial drug studies. The FDA concluded that "concern that expanded access will have a negative impact on drug development and review is not based on the evidence and is unwarranted."[7]
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> A subsequent FDA study found that, over a 10-year period encompassing nearly 11,000 expanded access requests, clinical holds were imposed in only two cases where adverse events occurred in an expanded access program. The holds were lifted in both cases.[8]

It should also be kept in mind that MAPs can speed clinical development and marketing authorizations. As shown by a number of published studies, the data collected via a MAP can identify patient subtypes that were not included in the clinical studies.[9,10] For example, a clinical study of Celgene's Vidaza (azacitidine) demonstrated the efficacy of the drug only in patients with a high risk of myelodisplastic syndrome (MDS). The study included too few low-risk patients to reach any conclusions about that population. Fortunately, data collected from a MAP indicated that the drug is also effective in patients with a low risk of MDS.[11]

Data collected from access programs can also be used to design patient-centric approaches for a treatment. For example, with a focus on sorafenib (Nexavar, Bayer Schering Pharma), Bellmunt and a panel of clinical advisors used a patient-focused schema and data generated from MAPs conducted in Europe and North America to determine the best treatment approach for various renal carcinoma subtypes.[12]

Some companies augment their clinical studies with MAPs. For example, the targeted receptor inhibitor drugs Tykerb (AstraZeneca), Gleevec (Novartis), and Iressa (AstraZeneca) were hailed as breakthroughs in the treatment of advanced-stage, multi-drug resistant cancer. While Phase 2 studies of these drugs quickly reached their enrollment targets, MAPs for the drugs enrolled 4,000, 7,000 and 24,000 patients, respectively. Large MAPs like these can produce statistically significant supplemental submission data.[13,14,15]

Do MAPs compete with clinical studies for scarce experimental medications?

In some cases, a biopharma can manufacture only a small or unpredictable amount of an experimental drug, so none is available for a MAP. If supply is a serious issue, the biopharma can defer initiating a MAP until the problem resolves or it can initiate the MAP with country caps on the supply available. The sponsor should disclose the limited supply up front to avoid potential public relations issues. In some cases, e.g., in an Ebola outbreak, the biopharma might have to reconsider its decision.

Conclusion

While a MAP might compete with a clinical study for patients, this issue can be mitigated with careful coordination. While patients receiving treatment in a MAP might have adverse events, studies have shown that the risk to a clinical development program or subsequent marketing authorization is negligible. While a MAP might compete with a clinical study for a scarce experimental medication, allocation of the drug is a business decision for management, and it can be handled with careful planning until sufficient drug supply is available.

On the other hand, a MAP can complement a clinical development program and, with the capture of information from treatment experiences, it can speed new drugs to the market and into formularies. This information can also help to identify new commercial markets to target, or new indications that the clinical development program did not identify.

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