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FDA Doubles Down on Efforts to Develop Guidance for Clinical Trial Stakeholders

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The US Food and Drug Administration has updated its Information Sheet on payments to clinical trial subjects, including travel reimbursements, and announced a public meeting on enrollment criteria, signaling the agency's commitment to addressing industry questions regarding the clinical trial process.

In late January, the US Food and Drug Administration (FDA) announced two actions that should be of interest to those involved in clinical trials. On January 29, the agency announced that it had published updates to the Information Sheet on Payments and Reimbursements to Research Subjects to clarify that reimbursement for travel expenses is acceptable. Then, the next day, FDA announced that a public meeting on clinical trial enrollment criteria will take place in April. These steps illustrate FDA's commitment to respond to industry concerns and questions, and to clarify the clinical trial process.

Payments and Reimbursements to Research Subjects

In the updated Information Sheet for Institutional Review Boards (IRBs) and clinical investigators, FDA explicitly stated that it does not consider reimbursement for travel expenses to and from a clinical trial site and associated costs, such as airfare, parking, and lodging, to raise issues regarding undue influence. Such expenses, however, must be reasonable, and would also be subject to IRB review.

However, FDA stated that IRBs should be sensitive to whether other proposed payments for participation could result in an undue influence, interfering with subject voluntary informed consent. While, as discussed by FDA, payments are not considered a benefit that would be part of the weighing of benefits or risks, such payments are recruitment incentives. Payments must be "just and fair," and must be reviewed by the IRB, taking into consideration the payment amount, method, and timing. Payments should not be contingent on study completion but small payments may be made as an incentive for completion of the study, so long as they do not unduly induce subjects to remain in the study when subjects may have otherwise withdrawn. All information concerning payments, including the amount and schedule, should be outlined in the informed consent form.

FDA stated that "[t]his update is in response to inquiries FDA received from stakeholders about appropriate reimbursement practices." Thus, while reimbursement for travel expenses is not a new occurrence in clinical trials, FDA's information sheet provides certainty regarding the agency's stance on the issue.

Public Meeting on Inclusion/Exclusion Criteria

In its *Federal Register* notice, FDA announced that a public meeting, titled "Evaluating Inclusion and Exclusion Criteria in Clinical Trials," would take place in April, with the purpose of "[bringing] the stakeholder community together to discuss topics related to eligibility criteria, their potential impact on patient access to investigational drugs, and the facilitation of diverse clinical trial patient populations." This meeting implements the mandate in the FDA Reauthorization Act of 2017 to convene a public meeting to discuss eligibility criteria and will inform FDA guidance on the same topic.

FDA's announcement states that "[a]mong other things, the public meeting will include discussion about various ways in which participation in clinical trials can be improved, including through alternative trial designs and

expanded access trials." FDA observed that the inclusion of relevant subpopulations in drug development programs will help to ensure that approved products will be safe and effective for the populations likely to receive the drug. However, clinical trial eligibility criteria can also exclude subgroups, resulting in trials not being fully representative of the broader patient population. FDA encourages diversity in clinical trial populations.

According to the announcement, discussion topics at the meeting will include the following:

- The risks and benefits of participation in clinical trials as well as potential regulatory, geographical, and socioeconomic barriers to participation.
- The rationale for eligibility criteria in clinical trials, as well as the impact of exclusion criteria on the enrollment of populations, such as infants, children, pregnant and lactating women, elderly, individuals with advanced disease, and individuals with co-morbid conditions.
- Alternative clinical trial designs that may increase enrollment of more diverse patient populations, while facilitating the collection of data to establish safety and effectiveness.
- How appropriate patient populations can benefit from the results of trials that employ alternative designs.
- How changes to eligibility criteria may impact the complexity and length of clinical trials, as well as the strength of data necessary to demonstrate safety and effectiveness.
- Opportunities for using data from expanded access trials.

When it comes to subject enrollment criteria, industry has had to wrestle with the dichotomous goals of ensuring that the relevant potential patient population is represented in the trial while also minimizing potential investigational product risks and confounding factors. By example, subjects who may be at greater risk for certain adverse events have historically been excluded from clinical trials. Clinical trial sponsors have also had to consider the impact that enrollment criteria could potentially have on the ultimate FDA approved indication, as stringent inclusion or exclusion criteria could result in labeled restrictions on the patient population. Through this public meeting, stakeholders will have the opportunity to share their views with FDA on these and other complex issues.

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