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Payments to Pediatric Subjects

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Federal regulations and guidances offer investigators limited help in determining payment to study subjects. The investigator and institutional review board (IRB) must use their judgment in establishing payments that are fair and equitable. Set them too high and they become coercive. Set them too low and they become exploitative, assuming anyone enrolls in the study. Pediatric studies raise additional questions about who gets paid and the form of the payment. The parent/child relationship introduces further complications.

Regulations and Guidances

The Code of Federal Regulations does not discuss subject payments. However, it requires that the possibility of coercion or undue influence be minimized for vulnerable persons such as children:

> An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. (21 CFR § 50.20)
>
> When some or all of the subjects, such as children, prisoners, pregnant women, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects. (21 CFR 56.111(b))

FDA's Guidance on Good Clinical Practice (ICH E6) discusses the disclosure and structuring of subject payments:

> The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified. (§ 3.1.8)
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> The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject. (§ 3.1.8)

FDA's Information Sheet, "Guidance for Institutional Review Boards and Clinical Investigators," discusses the rationale for, and method and timing of, subject payments:

> It is not uncommon for subjects to be paid for their participation in research, especially in the early phases of investigational drug, biologic or device development. Payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive. Financial incentives are often used when health benefits to subjects are remote or non-existent. The amount and schedule of all payments should be presented to the IRB at the time of initial review. The IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence [21 CFR 50.20].

> Any credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. Unless it creates undue inconvenience or a coercive practice, payment to subjects who withdraw from the study may be made at the time they would have completed the study (or completed a phase of the study) had they not withdrawn. For example, in a study lasting only a few days, an IRB may find it permissible to allow a single payment date at the end of the study, even to subjects who had withdrawn before that date.
>
> While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable to FDA, providing that such incentive is not coercive. The IRB should determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn. All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document.

Although the FDA recognizes that payments are an incentive, it provides no guidance as to when that incentive crosses the line into coercion or undue influence. It leaves that decision to the IRB, but presumably reserves the right to second-guess the IRB's judgments.

Payment Levels

Determining the amount of payment requires consideration of various factors, which vary from family to family and from study to study. Motivations often include access to experimental treatments, free medical care, learning about the disease and its treatment, and altruism. There may be no suitable conventional treatment. Family situations vary as well. For example, genetic diseases run in families.

If there is a direct benefit, e.g., staying alive, payment may be minimal or absent entirely. On the other hand, if there is no direct benefit to the subject, but only to future patients, payment should be larger.

Payment should reflect the burden on the subject and family:

- The number and duration of study visits
- Activities during each visit (risk, pain, discomfort and other demands on the subject)
- Travel time, inconvenience and costs
- Activities between visits such as diary completion and surveillance telephone calls

With pediatric studies, both parents and children must be motivated to participate. It is therefore necessary to distribute payments between parents and children. Most of the financial burden is likely to fall on the parents, but the child will suffer any pain or discomfort. It is hard to say in advance who will be more motivated by any health benefits or risks.

Children and their parents may disagree on participation in a study. Payment schemes should not exacerbate the conflict. Parents should not be encouraged to exploit their children financially. The child's wishes should be considered. However, depending on the functional age of the child, the parents may make the final enrollment decision. Balance is probably the best policy in most cases.

Should payment be higher for risky studies? Coercion is especially problematic in pediatric studies. Small children do not even understand the concept of death or "next week." What would they risk to receive a large, fluffy teddy bear? It seems hard to believe, but some parents will risk their child's health for a modest cash payment.

Should sites factor the difficulty of recruiting subjects into payment levels? For example, if enrollment will be easy, should payment levels be low? Are low payments exploitative? If enrollment will be difficult, should they be high? Are high payments coercive? Are low payments exploitative if competing studies also offer low payments? Are high payments coercive if competing studies also offer high payments? If a very poor family has, in effect, only one asset – a sick child – is it fair to minimize the payment for fear of coercion? If inadequate funding prevents a site from making what it deems to be fair payments, is it exploiting the subjects? Answers to these ethical questions are beyond the scope of this article, but the questions need to be considered by investigators.

Payment Forms and Methods

Most sites pay adult subjects (and parents) in cash or a close equivalent. Very young pediatric subjects, however, have no use for cash. When they become a bit older, even a shiny dime may be coercive. Given these possibilities, toys and gift cards may be more appropriate for pediatric subjects. Different payment forms and amounts may be appropriate for children of different ages in the same study.

Issuing checks and tracking payments can be more expensive than the value of the checks themselves, so simplicity is a virtue. Issuing a big check at the beginning of study will not promote subject retention. On the other hand, holding payment until the end of a study is coercive (unless it is a very short study).

Using gift cards requires advance purchases, so expiration dates may become an issue. They should be securely stored and tracked by serial number. Obtain receipts from families as if they were cash. They can be mailed like checks, but receipt cannot be confirmed unless the recipient signs in person.

Payments to a family exceeding $600 in a year require the site to file a 1099-MISC tax reporting form. The value of toys and gift cards must be included in the calculation, even if the child doesn't care for the toy or the gift card store. It is then a hassle for the family to document any offsetting travel or other expenses. On the other hand, reimbursing actual expenses creates a documentation burden for both parties. Gas cards and parking coupons are an option, but they have their own complications. And, of course, most study sponsors do not compensate sites for the time associated with paying subjects.

Examples

A few examples will clarify how the above principles can be applied in practice:

A. Clinical Trial A is an observational study of children between the ages of four and 12. There are seven 30-minute visits over a 12-month period. Each visit includes a two-page questionnaire for the parent and observation of growth and development of the child. There is no immediate benefit, but the information could be useful in the child's future healthcare. There is no risk.

   Payment: The child receives a small toy or game at the end of each visit, and a large toy or $20 gift card at the last visit. The parent receives a $25 check at each visit to help defray travel cost and inconvenience.

B. Clinical Trial B tests a drug on adolescents between the ages of 13 and 17. The drug is approved for adults but not for children, although there is substantial off-label use. For these reasons, this dose ranging study has minimal risk. The benefits are minimal for subjects with insurance, but significant for those without insurance. The study includes six visits over a six-month period. At the first and last visits, there are physical exams and blood draws. The other visits include a brief physical assessment

to determine drug tolerance and detect any adverse events. No invasive procedures are performed.

Payment: Subject payments are $75 for the first and last visit and $50 for each of the other four visits, totaling $350 Payments are by check to the parent with the understanding that they be shared equitably with the child.

C. Clinical Trial C compares two drugs previously approved for children. The purpose of the study is to determine which drug is most effective in children between the ages of eight and 17. Treatment is expensive and only partially covered by insurance, so the cost saving is a significant benefit. The treatment has risks, but the same risks as taking the drugs outside the study.

   Payment: There are no subject or parent payments.

Conclusion

While payments to adult subjects have challenges, pediatric studies raise additional questions about who gets paid and the form of the payment. Questions of coercion, undue influence and exploitation are especially complex given the parent/child relationship. In the absence of clear guidance from FDA or academic research, investigators and IRBs must use their own judgment as to what is fair and reasonable.

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