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Informed Consent Form Statements of Benefit

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The Belmont principle of Respect for Persons means that consent forms should include *all* the important information that potential study participants need to make an autonomous and informed decision on whether to participate. Consent forms should, therefore, discuss the potential benefits as well as the risks, so participants can decide for themselves whether the potential benefits they can expect of participation outweigh the risks as they understand them.

Institutional review boards (IRBs) are typically very cautious about how the benefit element in an informed consent form is written. They tend to require the statement to be realistic and directed to the reader (e.g., "you"), avoiding any statements that could be construed as promises or guarantees.

The Federal Code of Regulations states that consent forms should include "A description of any benefits to the subject or to others which may reasonably be expected from the research." (21 CFR 50.25(a)(1)(3)) (See Appendix A below for related FDA guidance.) As with statements of risk, benefit statements should be presented fairly, e.g., with respect to the likelihood of the benefit. There is no requirement that a study offer a personal benefit to the participant, but there must be a societal benefit, which must be stated clearly.

Investigators, study coordinators, research sites, study sponsors, CROs and the general public all benefit when people participate in clinical studies. People participate in clinical studies for a variety of reasons, both personal and societal.

Perceptions of "Benefit"

The sponsor's or investigator's perceptions of a study's benefits to participants might not be shared by the participants. Also, these perceptions are likely to vary from participant to participant.

Potential study participants might arrive at the informed consent meeting with objectives, needs and preconceptions that cause them to misinterpret or ignore written or verbal statements about benefits. For example, the study coordinator might say a benefit is "possible" but the potential participant might hear that it is "almost certain." It is therefore very important to confirm that the potential participant's understanding of the benefits is accurate.

In therapeutic studies, potential participants naturally expect some likelihood of direct medical benefit. IRBs thus want to see clear language in the consent form about the chance of medical benefit. They are very cautious about any statement that might falsely encourage potential participants to be optimistic, i.e., not entirely objective. However, therapeutic misconceptions can be very resilient. It is common for potential participants to conclude that, even with a low probability of direct medical benefit, their *personal* likelihood is much higher because they are a good person, it's their last option, it's time for their luck to turn, they have a positive attitude, "hope will triumph," they will be the perfect study participant, "where there is a will, there is a way," a higher power is watching over them, etc.

When considering the personal and societal benefits of participating, people can under- or overemphasize the fact that the investigator, study sponsor, CRO and other parties also

expect to benefit from the study. Some people are unwilling to participate in clinical studies because they assume the study sponsor and other parties care nothing about the participants and have only their own interests in mind. On the other hand, many patients believe their physician would not be offering a study unless he or she believed it would benefit the patient, no matter what the consent form says.

When writing a consent form or preparing for a consent discussion, it is important to be aware that a potential participant is likely to be filtering the words through one or more of these biases and misconceptions, likely without even being aware of their presence.

Possible Benefits to Study Participants

From the participant's point of view, the benefits of participating in a clinical study can include the following:

- Obtain treatment — perhaps even a cure — for the medical condition being studied, i.e., as an alternative form of clinical care.
- Learn more about the medical condition being studied.
- Obtain more tests, assessments and attention than a patient outside the study would receive.
- Obtain care that would not otherwise be affordable to the participant.
- Discover an unknown medical condition (an "incidental finding"), unrelated to the study.
- Help create knowledge that will help the participant, his or her family, or future patients with their medical condition.
- Obtain cash stipends or compensation.
- Satisfy their curiosity about the clinical study experience.
- Enjoy a diversion from the routine of their day-to-day life.

We cannot presume to know what motivates a specific person to participate in a study — we need to ask. We can then discuss their expectations to ensure — to the extent possible — that their expectations are realistic.

Possible Benefits to "Others"

As stated above, the Federal Code of Regulations requires consent forms to include "a description of any benefits to the subject or to others which may reasonably be expected from the research." Who are the "others" and what benefits might they derive? Current and future patients are the most likely to benefit directly from a clinical research study through potential new treatments and a better understanding of the medical condition. The general public might benefit through an increase in generalizable scientific knowledge. The study sponsor, CRO, investigator and others expect to benefit, but they are not usually considered in this requirement.

Acceptable Statements about Benefits to Study Participants

Once we accept the above rationale for informing people about the benefits of study participation — and the likelihood that not everyone perceives benefits equally — we then need to put the benefits into words that are objective, accurate and understandable. In general, most benefits are "possible" or "likely" but not "guaranteed." The following statements can be adapted, as appropriate:

If random selection puts you in the group that receives the experimental vaccine, the treatment might reduce the chance that you will contract the flu this year. However, we won't know how well the experimental vaccine has worked — or if it has worked at all — until after the study is over.

If random selection puts you in the group that receives the experimental study drug, it might help you control your insulin levels. However, it will not cure your diabetes. We will not be able to reach any firm conclusions about the benefit, if any, until after the study is over. Any benefit will end when you complete the study.

In previous studies, some people who received the study drug have seen their asthma improve during the course of the study. We do not know whether they returned to their previous state of health after the study; nor do we know whether you will receive the study drug or whether the previous studies are even relevant.

The experimental drug that the study will add to your regular blood-pressure medication might further lower your blood pressure.

To test the experimental drug, we will perform procedures, tests and assessments that you might not be receiving now to manage your high blood pressure. You might find these additional activities burdensome or you might consider them an advantage.

We will perform a variety of lab tests. With your permission, we will share with your physician those tests that have been validated for use in clinical care. Such tests may or may not help your physician care for you. If your physician does follow up on them, it might result in an additional cost to you.

If we discover a problem with your health that you did not previously know about and that can be treated, we will discuss with you the problem and your options for obtaining treatment. If this happens, you might have to leave the study.

If you are in the control arm, you will receive [drug], a drug that the FDA has approved for psoriasis. Your physician might prescribe the same drug — or a different drug — without you having to participate in the study.

The purpose of this study is to see if the experimental drug works better than a placebo (a sugar pill). Depending on the study's results, future patients might benefit from this knowledge.

We will collect a tissue sample from you and make it available to scientists that study lung cancer and other forms of cancer. They might learn things from your tissue sample that will not benefit you directly but might benefit future patients.

Financial "Benefits"

Most potential participants are interested in the financial aspects of study participation: How will it impact my employment? Will my out-of-pocket costs be reimbursed? Will it save me money on clinical care? Who will pay for childcare, travel, hotel? Will I have to pay to participate in the study, or will the study pay me? Who will pay for my medical treatment if I am injured in the study?

We downplay cash stipends and most other financial matters (except in Phase 1 studies) because we do not want them to be considered in the IRB's or the participant's risk/benefit calculation. A good option is to cover these matters in a separate "Financial Matters" section.

The following language can be adapted, as appropriate:

> As a study participant, there will be no cost to you for any study procedures, tests or assessments. You will receive a $50 cash payment per visit in consideration of your time and inconvenience, plus $100 upon your completion of the study. We will also cover reasonable childcare, parking and transportation costs based on receipts you provide us.

Small completion bonuses are acceptable to the FDA. Any such bonus should not be so large as to unduly influence participants to stay in the study. Potential participants might ask for a mileage allowance, which is not exactly an out-of-pocket cost, or payment to a relative for childcare. The consent session should clarify any such issues.

> Some of the procedures, tests and assessments might replace procedures, tests and assessments that you and your physician would still want to perform in the absence of this study. If so, by participating in the study, you might save out-of-pocket costs or insurance copays.

This provision can probably mention specific procedures, tests and assessments.

> If you are homeless, we will offer you a nutritious meal and a shower at each study visit.

This benefit is similar to a cash stipend, so it could be considered a recruitment inducement. It could also be covered in the description of study visits.

Why Are Some IRBs More Cautious than Others?

As mentioned above, IRBs tend to cautious. There are likely two causes: The IRB's mission and learned responses.

Mission

Per the regulations, the IRB's sole mission is to protect the study participants in the context of the risks and potential benefits of the research. IRBs see themselves as the only eyes reviewing the study without conflict; their role is to guard the consent process from the optimism and self-interest of all the other parties, including potential participants. IRBs are thus naturally more interested in eliminating overly positive language than in finding ways to make a study more attractive to potential participants. Some IRBs are just more cautious than others, perhaps because of their institution's culture or the expertise or personalities of the members.

Learned Response

Experience teaches IRBs to be cautious. When an attorney writes a contract and his or her client is later burned by a loophole, the attorney's natural response is to close that loophole in future contracts. The new language will become part of the attorney's standard template, even if the problematic incident never arises again.

The same thing happens with IRBs: When something goes wrong in a study that an IRB has approved, it is natural for the IRB to want to avoid similar problems in the future. Every IRB runs into different problems. Their interpretations and remedies can vary. Their institutional memory can vary. As a result, the sensitivity of IRBs to particular issues will diverge over time.

For example, an IRB member who has heard that an investigator made exaggerated claims about benefits in the consent discussion might see very conservative benefit language in the consent form as a way to rein in overpromises in the consent discussion.

Conclusion

Potential study participants deserve to receive *all the important information*, including potential benefits, that is pertinent to their decision to participate. Information about benefits must be worded to be objective, accurate, understandable and resistant to therapeutic misconception.

Most IRBs review benefit statements with caution — often more caution than the investigator might consider justifiable. Investigators should assess their IRB's level of caution and any special concerns. Nevertheless, most IRBs are open to discussing the merits of benefit statements that they find questionable.

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Appendix A. FDA Guidance

FDA's "A Guide to Informed Consent – Information Sheet" says:

> In seeking informed consent, the following information shall be provided to each subject:… (3) A description of any benefits to the subject or to others which may reasonably be expected from the research.
>
> The description of benefits to the subject should be clear and not overstated. If no direct benefit is anticipated, that should be stated. The IRB should be aware that this element includes a description not only of the benefits to the subject, but to "others" as well. This may be an issue when benefits accruing to the investigator, the sponsor, or others are different than that normally expected to result from conducting research. Thus, if these benefits may be materially relevant to the subject's decision to participate, they should be disclosed in the informed consent document.

FDA's "Informed Consent Information Sheet (Draft Guidance)" says:

> The description of potential benefits should be clear, balanced, and based on reliable information to the extent such information is available. This element requires a description of the potential benefits not only to the subject (for example, "This product is intended to decrease XXX; however, we cannot guarantee that you will benefit"), but also to "others" (for example, "your participation in this research may not benefit you but may benefit future patients with your disease or condition"). Overly optimistic representations of the clinical investigation may be misleading and may violate FDA regulations that prohibit promotion of investigational drugs and devices (see 21 CFR 312.7 and 21 CFR 812.7). Because the purpose of the study is to determine the safety and/or effectiveness of the test article compared to the

control, it is not yet known whether the test article may or may not provide a benefit.

FDA considers payment to subjects for participation in clinical investigations to be compensation for expenses and inconveniences, not a benefit of participation in research. If payments are provided, the consent process should not identify them as benefits.

FDA's "Payment to Research Subjects – Information Sheet" says:

The Institutional Review Board (IRB) should determine that the risks to subjects are reasonable in relation to anticipated benefits [21 CFR 56.111(a)(2)] and that the consent document contains an adequate description of the study procedures [21 CFR 50.25(a)(1)] as well as the risks [21 CFR 50.25(a)(2)] and benefits [21 CFR 50.25(a)(3)]. 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.

