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WHITE PAPER

# 10 Tips for Writing Compliant Participant Materials

Recruitment materials are a potential participant's first introduction to the study, and post-consent materials can influence an individual's decision about continued participation. It is important to adhere to the principles of subject protection—that is, allowing subjects to make informed decisions about what is in their own best interest—with the materials that appear at the earliest stages of recruitment as well as through the life of the study.

## Topics

- Abiding by the Belmont Report
- Regulatory framework and best practices
- Advarra's approach
- Protecting vulnerable populations
- Problematic language to avoid

## Background

Subject-facing materials are defined most broadly as any study-related content other than the informed consent form with which the participant interacts, whether delivered in written, audio, or audiovisual format. Commonly used subject-facing materials include:

- Recruitment materials, such as flyers, posters, brochures, letters, website,* or social media postings
- Radio or television spots
- Screening tools delivered over the phone, internet, or face-to-face at a screening visit
- Subject questionnaires, diaries, and medication logs designed to collect outcomes data or track compliance
- Study brochures describing the study in greater depth
- Reminder letters and encouragement and gratitude letters designed to reduce attrition
- Instruction cards or pamphlets pertaining to the study intervention

## Regulatory Framework and Best Practices for Reviewing Subject-facing materials

While the regulations 45 CFR 46 and 21 CFR 50 and 56 are verbose with respect to informed consent, they are less prolix about subject-facing materials. At the same time, other regulatory authorities provide clear guidelines for reviewing and approving subject-facing materials. Current guidance about recruitment materials incorporates the notion that potential study participants are a priori vulnerable to coercion, undue influence, and therapeutic misconception.

### FDA guidance documents expand upon these concerns:

The FDA "considers direct advertising for study subjects to be the start of the informed consent and subject selection process." It goes on to say that IRB review must evaluate the materials to assure that they are "not unduly coercive and [do] not promise a certainty of cure beyond what is outlined in the consent and the protocol. This is especially critical when a study may involve subjects who are likely to be vulnerable to undue influence."[6]

FDA guidance also recognizes that coercion and undue influence can stem from specific language (for example, implying a cure) as well as from the way information is presented. Thus, "advertisements should not promise 'free medical treatment' when the intent is only to say subjects will not be charged for taking part in the investigation…[and] may state that subjects will be paid, but should not emphasize the payment or the amount to be paid, by such means as larger or bold type[6]." By the same token, radio and television spots should not announce compensation amounts at a higher spoken volume or with large or otherwise eye-catching graphics.

The FDA states a general belief that advertisements should be limited to the amount of information prospective subjects need to determine their eligibility and interest; the time commitment required of subjects; and basic location and contact information for the research site.[6]

The Office of Evaluations and Inspections (OEI) is one of several components of the Office of the Inspector General (OIG). In June 1998, the OIG/OEI identified weaknesses in the system intended to protect human subjects and undertook a multifaceted approach to understanding the problems. It surveyed 200 IRBs (as well as other stakeholders, such as the FDA), conducted extensive literature reviews and site visits, and reviewed US federal regulations and the Canadian Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans.

Based on an analysis of the data from these diverse sources, the OIG/OEI issued a report in 2000 that provides guidance on best practices for recruiting human subjects. With respect to recruitment materials, the report states, "[R]ecruitment is a vital first step in the consent process, one that must not in any way be coercive or misleading to the potential subjects," and that "…misleading information may shape subjects' initial judgement about a research study and thus may influence decisions about participating. This is viewed as eroding the value of the informed consent process."[7]

Additionally, the OIG/OEI noted that the Department of Health and Human Services (DHHS) provided little guidance to IRBs on acceptable recruitment practices and, as a consequence, left many IRBs confused about what lies within their jurisdiction of authority and whether and how they may register objection to recruitment practices they find troubling.


## Advarra's Approach to Reviewing Subject-Facing Materials

The Advarra IRB's review of Subject-facing materials for compliance derives from informed consent regulations, the guidance documents that are available, and common sense.

Our principal concerns are that the subject-facing materials avoid promoting a therapeutic misconception and do not use language that is unduly influencing or overly reassuring. Each of these concerns will be discussed below. However, it is worth mentioning that we draw some distinctions between pre-consent subject-facing materials and post-consent subject-facing materials.

When reviewing pre-consent subject-facing materials (e.g., materials used in recruitment and screening activities as well as some study brochures, pamphlets, or web content), we are especially concerned with protecting autonomy, comprehension, and voluntariness, taking to heart OEI's description of recruitment as a form of early consent.

Before the consent process, the subject does not have sufficient information (or opportunities to ask clarifying questions) to allow them to make an autonomous and "fully" informed decision about participation.

Post-consent, the subject has been informed of the risks and benefits of participation and, we feel, is less susceptible to misinformation or misconception. While we are still concerned with protecting autonomy, we become additionally concerned with protecting privacy post-consent.

### Avoiding therapeutic misconception

Many research studies are conducted in a medical context. Investigators are often doctors in white coats; investigational sites are also hospitals; and clinics and research participants may also be patients with medical conditions. In this setting, it is natural that participants do not realize that the goal of research is not primarily their well being, but more general knowledge that may benefit many, and that the researcher is not acting as "their doctor."

While this "therapeutic misconception" is pervasive, subject-facing materials should not take advantage of the misunderstanding to knowingly recruit individuals who otherwise might not be interested in research participation.

Therapeutic misconception is described in a seminal 1982 paper by Appelbaum et al. Appelbaum writes, "[U]nless otherwise informed, research subjects will assume (especially, but not exclusively, in therapeutic research) that decisions about their care are being made solely with their benefit in mind."[8]

Appelbaum's paper closely followed the publication of the Belmont Report, wherein practice and research were delineated and practice was defined as "…interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success."[3]

His work elucidates how pervasive and intractable therapeutic misconception is in the context of research: even when subjects are explicitly informed about scientific design and methodology (including randomization, double-blinding, and placebo controls) and demonstrate an understanding of these principles, they will fabricate a therapeutic basis for the research process, or otherwise appear "not to hear, to distort, or to deny what was

revealed to them." Appelbaum points out that this misconception is "a critical handicap to the subject's ability to engage in an accurate assessment of benefits and risks" and thus to making an informed and autonomous decision in their own best self-interest.[8]

### Avoiding language that is unduly influencing

In the discussion of voluntariness, the Belmont Report states specifically that the element of voluntariness in informed consent "requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate, or improper reward or other overture in order to obtain compliance. Also inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable."[3]

These undue influences can take the form of exerting relationship power as well as through offers of monetary or other pecuniary inducements. In Belmont, vulnerable subjects are considered to include both the very sick and the economically disadvantaged, and the following caution is made:

The relationship between low socioeconomic status and lower levels of education further militate against enrolling from a population that might be more likely to be influenced by money and also less able to comprehend information about the study.[3]

### Avoiding language that is overly reassuring

This reassurance can take the form of minimizing risks or exaggerating benefits in a way that is more subtle than promoting a therapeutic misconception. At the heart of the IRB's concern, however, remains our intention to avoid biasing potential participants toward enrolling in a study, perhaps against their best interests.

## Stories From the Trenches: 10 Tips for Writing Compliant Subject-Facing Materials

The following are examples from subject-facing materials that we concluded promoted the therapeutic misconception or included language that was overly reassuring or unduly influencing. We also include examples of practices that compromise privacy and/or autonomy. While this list of examples is clearly not exhaustive, it represents the issues that arise most frequently and/or those that cause particular consternation during IRB review.

### 10. Vulnerable populations

DHHS regulations that define the criteria for IRB approval of research note specifically that the IRB "…should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons." They go on to say: "When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as [the vulnerable populations listed above], additional safeguards have been included in the study to protect the rights and welfare of these subjects."[5]

The mandate for protecting vulnerable participants in research stems from the idea that the degree of autonomy necessary to consent to study participation may be diminished by participants' circumstances. Yet, their participation in the research process is important, as they deserve to benefit from, as well as share the burden of, the research. Belmont advises, "The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations."[3]

While additional protections of the vulnerable populations of pregnant women, prisoners, and children are codified under the regulations at subparts B, C, and D respectively, the remaining populations, including economically or educationally disadvantaged people, do not enjoy special protections. The nidus of concern reflected in the phrase "…vulnerable to coercion or undue influence" informs the Advarra's review of subject-facing materials.

Appropriate safeguards are necessary to protect vulnerable populations from harm as they exercise their autonomy in deciding whether to participate or to continue participation. In addition, assumptions about the unsuitability of certain vulnerable groups for research

should be minimized (e.g., physically disabled or non-English speaking).

Recruitment and study materials require the same safeguards as may be included in the protocol and consent forms. The table on the following pages describes common vulnerable populations and ways that subject-facing materials can ensure adequate protections, but it is not an exhaustive list of groups that may require special consideration in research.

| Vulnerable Group | Minimum Protection | Examples |
|---|---|---|
| **Employees and their family members** | Study participation is not required as an employee or a family member of an employee, and neither decision (to enroll or to not enroll) will impact employment. | Participation should be anonymous so that employers and fellow employees are not aware who is participating in the study. Posters or emails regarding participation should not tap into feelings of loyalty or responsibility toward the company. Compensation or reimbursement amounts should not be unduly influencing. Study procedures should be done in a discreet, private setting or in an offsite location. Reminders regarding voluntary participation should be given. |
| **Children and minors** | Parents or legal guardians must be involved to protect the child, make necessary decisions, and give permissions. Children must be allowed to exercise autonomy according to their capacity and provide ongoing, affirmative agreement (assent) to participate in research.4 | Advertisements targeting adolescents should be clear that parents will need to answer screening questions, give permission for study participation, and be involved as the study progresses. Unduly influencing statements that imply the study will solve health problems, save participants from communicable diseases, or give them quick relief should be avoided. Compensation and retention materials should not entice a minor to join or remain in the study when they might not otherwise do so (e.g., a device with game apps that can be kept after the study is over, compelling toys given at each visit). Language that minimizes risk should be avoided (e.g., "It won't hurt because our nurses are great!"). |
| **Adult participants unable to read (e.g., blindness, illiteracy)** | Accommodations are required so that the non-reader has the same level of understanding regarding participation as someone who can read for themselves. An impartial witness attests to the apparent understanding of the potential participant and accuracy of the information relayed. | Participants who are non-readers should be included in research unless their participation would cause undue burden, harm, or compromise data collection. It is possible that multiple questionnaires or diaries might impose a burden or not provide reliable data. Issues around participation can be assessed on a study-by-study and case-by-case basis. |

| Vulnerable Group | Minimum Protection | Examples |
|---|---|---|
| **Non-English speakers** | Non-English speakers may share in the potential benefits and burdens of participation. All study materials and resources available in English are to be provided in the speaker's preferred language. An impartial interpreter is provided for conversations. | Every effort should be made to include non-English speakers in research studies according to the site's location in the community and the potential non-English speakers in the area. Approved English recruitment and participant materials should be translated, along with consent forms and patient-reported outcome (PRO) measures. Targeted advertising can include this group of potential participants. |
| **Adults requiring LAR due to diminished decisionmaking capacity** | Participants who are not competent to provide consent for themselves must have a legally authorized representative (LAR) to make decisions on their behalf. Even so, the participant must also provide affirmative assent upon enrollment and for the duration of the study. | Depending on cognitive abilities, recruitment for this group may target both the participant and caregiver. It is important to be clear about the time commitment and effort involved in participating for both the participant and caregiver, as this may be an undue burden for some. |
| **Pregnant women** | When pregnant women are approved to participate in research, they need to be informed of all the possible risks known (and the possibility of risks unknown) for both themselves and the fetus. | Diagnostic studies should consider a pregnant woman's concerns about her pregnancy when designing recruitment materials to avoid undue influence. |
| **Economically disadvantaged** | Compensation and reimbursement should be adequate for the time and effort given for participation, but should not induce an individual to join or continue in a study when they might otherwise decide to end participation. | Depending on cognitive abilities, recruitment for this group may target both the participant and caregiver. It is important to be clear about the time commitment and effort involved in participating for both the participant and caregiver, as this may be an undue burden for some. |
| **Physically disabled** | Physical limitations should not be a barrier to study participation. | Participant materials with larger fonts, wheelchair accessible scales, hip chairs, and electric doors are examples of measures that could make study participation easier for this group. Non-hearing individuals can also be enrolled, if appropriate, with ASL interpreters. Recruitment materials can advise of accessible facilities so potential participants will not self-select out of the study for accessibility issues alone. |

## 9. Translations

The regulations at 21 CFR 50.20 and 45 CFR 46.116 state:

> *"The information that is given to the subject or the representative shall be in language understandable to the subject or the representative."*[4,5]

At Advarra, the IRB requires that all materials with which a non-English speaking subject will interact—including informed consent or assent forms, diaries, questionnaires, and recruitment materials—be translated into the subject's primary or preferred language. We require the translation be done by a qualified translator and that a valid translation certificate be provided to verify that the translated document is an accurate representation of the source document.

When an official translation certificate is not obtainable, a document attesting to the validity and accuracy of the translation from the sponsor, CRO, or institution is required along with rationale for why a standard certificate cannot be obtained.

Situations have arisen in which a subject's family member or a site's staff member acted as the translator. In these circumstances, the IRB requires the site to obtain a valid translation of the source document, re-consent the subject (or otherwise provide translated materials) with the aid of an impartial interpreter, and provide us with a written explanation for their failure to consent appropriately and to obtain properly translated materials.

## 8. Participant Reported Outcomes

Patient-reported outcome (PRO) instruments may be used as primary source material for efficacy endpoints and to collect ancillary information that is used to support labelling claims. These PROs, which we classify as post-consent subject-facing materials, may comprise validated questionnaires, subject diaries, and the like; as source material, these may be sent to the sponsor for data entry.

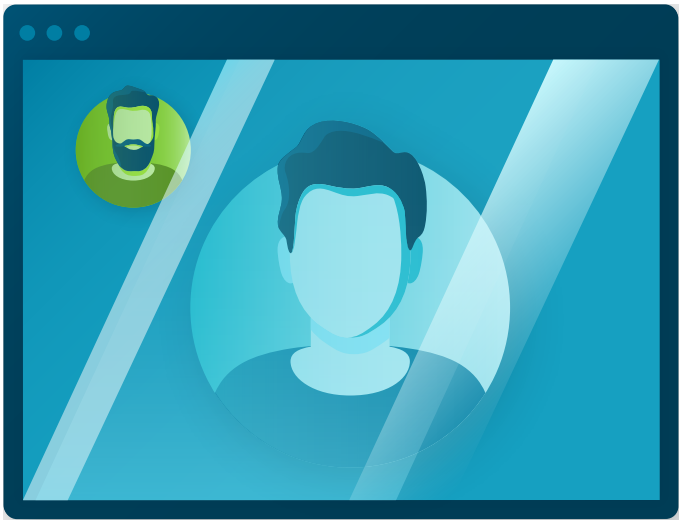
A tension exists between satisfying the need to verify a subject's identity on the documents (conferring attributability, which bears upon data integrity) and the need to protect subject confidentiality. This raises the question of whether these PRO instruments may be sent to the sponsor without redacting the subject's identity.

FDA regulations do not address how to adequately attribute PRO instruments while simultaneously maintaining confidentiality. However, the regulations do stipulate that the informed consent form needs to inform subjects that their records will be seen by the sponsor/sponsor representatives and possible FDA authorities as well.

An FDA Q&A document states:

> *"Therefore, it would not be completely improper for the sponsor to receive subject data with the identifiers intact—they would, however, then have the onus of protecting the confidentiality of that information."*[9]

While the IRB would prefer to have subject identity redacted, at Advarra we recognize that at times this can be contrary to study aims. Our position is that we will allow subject identifiers on post-consent subject-facing materials such as PRO instruments as long as we can verify that the consent form forewarns subjects of the potential for sharing their information.



## 7. Phone screening

Advarra takes the position that once a potential participant has begun to interact with a phone screener (particularly a live screener, as opposed to an online form), the potential participant develops a sense of obligation to complete the process and could experience difficulty disengaging, even if they are uncomfortable answering sensitive questions. For this reason, if a screening script contains sensitive questions (for example, about substance use, mental health, or illegal activities), we request that potential participants be alerted at the outset. In general, we expect that the study be described first and ongoing interest ascertained before raising the issue of sensitive questions. The language we recommend is as follows:

> *"In order to determine if you qualify for this study, I will need to ask you some personal information about your health and lifestyle, including questions about [your mental health] and [your drug and alcohol use] and [HIV status] and [and other sensitive topics as appropriate]. You do not need to answer any questions that you do not want to answer and you may end this call at any time. May I proceed?"classify as post-consent subject-facing materials, may comprise validated questionnaires, subject diaries, and the like; as source material, these may be sent to the sponsor for data entry.*

## 6. Avoid unduly influencing language

Per the OIG/OEI report: "Ads also should not overly stress any payment, monetary or otherwise, offered to subjects lest they be considered coercive to the subject."[7]

At Advarra, the convened IRB reviews and adjudicates compensation, which is then committed to language in subject-facing materials. Compensation amounts may not be ambiguous. Per federal guidance, compensation should not be highlighted in subject-facing materials (i.e., made visually prominent, or audio-recorded at a higher volume than other audio-recorded material). Compensation must never be listed specifically as a benefit.

Examples of language and formatting to avoid is below, including examples provided by the FDA. (Quotation marks indicate language used in the ad.)

| Problematic Language | Replace With or Change To |
|---|---|
| "Free" (e.g., study medication will be free) | "At no cost" |
| Compensation amount in bolded font or placed first or early in the material | Un-bold font, move to a less conspicuous position in the materials |
| "Make your acne pay!" or otherwise offer a chance to earn money | Delete entirely |
| "…may be compensated up to $XXX." | Site compensation amounts must be approved, specified, and must match the language in the consent form. Model recruitment materials may contain placeholders if compensation will vary across sites. |
| "Free medical exam." | "Study-related exam" |
| "Reduces stress involving insurance, copays…" | "Study-related care and study drug at no charge," or "No insurance required." |

## 5. Avoid overly reassuring language

Language that attempts to downplay the impact or magnitude of foreseeable harms is viewed as being overly reassuring.

| Problematic Language | Replace With or Change To |
|---|---|
| "…and is safe," or "side effects are manageable" | Delete entirely |
| "[XYZ procedure] is painless," or "You cannot feel [XYZ procedure] at all" | "In previous studies, participants stated…" |
| "Make your acne pay!" or otherwise offer a chance to earn money | Delete entirely |
| "[XYZ procedure] is non-invasive and painless" | Delete "painless"<br><br>Revise flip charts, brochures, etc. to match risk language in the consent form |
| "...gentle electrical stimulation" | "Small electrical pulses" |
| "Involves a minor procedure" | "Involves an investigational procedure" |

## 4. Avoid therapeutic misconception

One source of therapeutic misconception is the portrayal of an investigational product as a proven therapy or treatment. We mitigate this risk by qualifying the words "drug," "medication," "treatment," or "relief" with the words "investigational" or "study."

| Problematic Language | Replace With or Change To |
|---|---|
| "Drug" or "medication" | "Investigational drug" or "investigational medication" |
| "Potential new medication" | "New investigational medication" |
| "Potentially relieve [condition]" | "Investigational drug for [condition]" |
| "Medicine for the treatment of [condition]" | "Investigational medicine for [condition]" |

## 3. Avoid unduly influencing language

At Advarra, the IRB routinely modify language implying that a potential participant's only or best hope is to enroll in a clinical trial.

| Problematic Language | Replace With or Change To |
|---|---|
| "Participating may not only bring you hope, but also improve your symptoms." | Delete entirely |
| "Be part of a cutting-edge program." | "Join an investigational program for [condition]." |
| "You may be at risk for a life-threatening infection." | "You may be eligible for a research study." |
| "We want to help you!" | "You may be interested in a research study for…" |
| "Tired of dealing with the pounding pain?" | Delete entirely |
| "Do you want to help your children adjust to divorce?" | "Join a research study investigating how children adjust to divorce." |
| "We're worried about these chemicals…" | "We're testing for these chemicals…" |
| "Exciting clinical trial" | "Clinical trial" |
| "[Product] is not available outside of the research study." | Delete entirely |

## 2. Avoid overly reassuring language

In addition to implying a certainty of beneficial outcome, overly reassuring language can imply safety and portray the research enterprise as exalted (thereby emphasizing an altruistic benefit).

| Problematic Language | Replace With or Change To |
|---|---|
| "approved by an IRB/ regulatory body" | "reviewed by an IRB/ regulatory body" |
| "to help keep volunteers safe" | "to protect the rights and welfare of research participants" |
| "empower patients to decide" | "offer an alternative to the standard of care" |
| "carefully controlled/ monitored/conducted" | "controlled/monitored/ conducted" |
| "make sure it is done correctly" | "monitor how it is conducted" |
| "Only treatments that are shown to be safe in laboratory tests can be tested in people." | Delete entirely |
| "Your safety is our top priority." | "We are concerned about your safety." |

## 3. Avoid unduly influencing language

Per the OIG/OEI report: "[Stakeholders] consistently expressed their frustration to us over seeing ads they considered misleading...for example, when it implies that an investigational drug is treatment rather than research"; and "The blurring of research and treatment, often referred to as 'therapeutic misconception,' can be difficult to clarify once a potential subject's initial impressions have been formed."[7]

The words "treatment," "therapy," "doctor," and "medical" each promote therapeutic misconception. The table below indicates misleading terms and our preferred language.

| Problematic Language | Replace With or Change To |
|---|---|
| "Treatment" | "Research study," "Study medication," "Investigational drug" |
| "potential treatment for [condition]" | "investigational drug/cream/ procedure for [condition]" |
| "to treat [condition]," "medication to treat [condition]" | "for [condition]," "study medication for [condition]" |
| "treatment period/ phase" | "study-drug dosing period/phase" |
| "treating patients with" | "providing the study medication to" |
| "a good treatment option" | "an option available to you" |
| "treatment,""treatment dose," "therapy" | "study drug dose," "dose of investigational medication," "investigational drug" |
| "treated by" | "seen by" |
| "doctor," "nurse" | "study doctor," "study staff" |
| "for [doctor's] review" | "information about the clinical trial" |

| | |
|---|---|
| "medical professional" | "study doctor," "study team," "study staff" |
| "specialists/experts" | "study doctor experienced in [area of expertise]," "researchers," "study physicians" |
| "free medical exam" | "study-related exam at no cost to you" |

## Conclusion

Subject-facing materials are a potential clinical research participant's first introduction to a study, and the information the materials contain establishes—if not finalizes—comprehension of and expectations for a study.

Given the power subject-facing materials hold to help a potential participant choose to begin and continue participating in research, it is paramount that they uphold the tenets of the Belmont Report at all times in the research process, from recruitment through the close of the study. It is our hope that this white paper provides a strong foundation for researchers to do so.

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