

Clinical Researcher

July 2021

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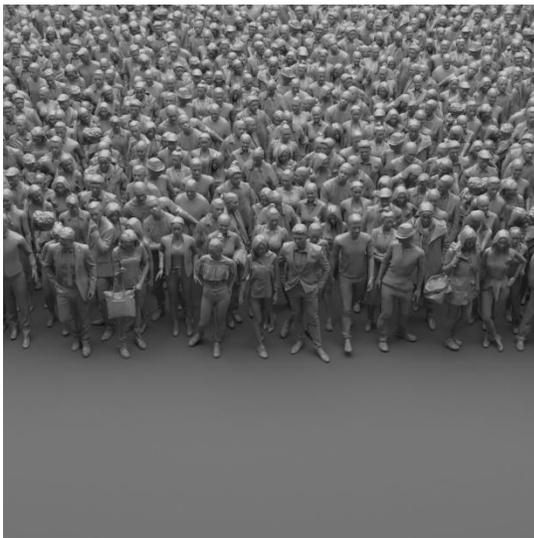
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SPECIAL FEATURE

Consent Process Best Practices for Special Populations to Reduce Perceived Pressure to Participate in Clinical Trials

Sean Horkheimer, JD, CIP



When recruiting participants for a clinical trial, the U.S. Department of Health and Human Services (HHS) regulations require that “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” (see 45 CFR 46.116 in the [Code of Federal Regulations](#)). Coercion occurs when there is an explicit or implied threat of harm

used to obtain compliance. Undue influence occurs when an offer of an excessive reward or other benefit is used to obtain compliance.

Whether a potential clinical trial participant is vulnerable to coercion and/or undue influence is often situational. A potential participant may be vulnerable in one situation but not in another; this will depend on the context of the participant’s involvement and the relationship between the participant and the study team. For example: college students may be vulnerable when recruited for research conducted by their professors due to the power imbalance between the parties, but would not be considered vulnerable when recruited for research that is unrelated to their education or status as a student.

Coercion and undue influence can result in a situation where a potential participant feels pressured to enroll in a clinical study. This perceived pressure undermines a potential participant’s autonomy and ability to provide meaningful informed consent. Some participant

populations are more susceptible to this pressure based on their unique circumstances—prisoners, military personnel, elderly patients in residential healthcare settings, and students can all face additional pressure to participate when asked to enroll in research.

In the case of prisoners and military personnel, the regulations directly address this situation by imposing additional requirements for study teams and institutional review boards (IRBs). In the other cases, the consent process can be designed to minimize the participant's perceived pressure to enroll.

Let us examine the regulatory requirements and consenting best practices for these participant populations.

Prisoners

Prisoners are involuntarily confined or detained individuals in a penal institution (45 CFR 46.303(c)). Compared to non-prisoners, they have very little control over their daily activities. Prisoners are also subject to punishment by correctional officers for any misconduct or violation of strict prison rules. In this precarious situation, they have greatly reduced autonomy and are vulnerable to coercion and undue influence.

Subpart C of the [Common Rule](#) (Federal Policy for the Protection of Human Subjects) enacts additional regulatory protections for participants who are prisoners (45 CFR 46.301 et seq.). IRBs can only approve research that falls into specifically delineated categories (45 CFR 46.306(2)). To prevent undue influence, enrollment should not provide the participant with advantages in terms of living conditions, medical care, quality of food, amenities, and opportunities for earnings compared to the regular prison population that are of such a magnitude they undermine the potential participant's ability to effectively evaluate the risks of the research (45 CFR 46.305(a)(2)). To prevent coercion, the consent process should inform potential participants that their involvement will have no impact on decisions made concerning their possible parole (45 CFR 46.306(a)(6)).

Aside from these regulatory requirements, there are some consent process best practices that can reduce a prisoner's perceived pressure to participate. Members of the study team should identify

themselves and their relationship to the prison at the start of the consenting process. If the study team includes members who are employees of the prison system, they should consider whether the person obtaining consent should be someone independent.

The warden and any prison administrators who have the ability to punish or reward participants should not be present during the consenting process, if possible. Their presence could be perceived as a subtle form of intimidation or possible promise of better treatment that will impact a potential participant's decision to enroll in the research.

The consent form should outline the extent to which prison officials will be able to access and review the research records. Participants will be interested to know if they will be identified individually or if results will be collected and stored in aggregate form. If the research is designed to examine prohibited activities taking place in the prison system and participant anonymity is essential to protect the participant's rights and welfare, the consent process for each individual participant should take place in private, outside the view of other inmates or correctional officers (this may also extend to the research activities, if necessary to protect participant privacy).

Military Personnel

In many ways, military service is defined by rigid hierarchies, deference to authority, and the expectation that all orders from the chain of command are followed. As such, military personnel can feel additional pressure to participate in research when it is presented to them in the context of their service.

Federally funded research recruiting military personnel is governed by the Department of Defense (DoD) regulations (32 CFR 219.101, DoD's adoption of the Common Rule). Additionally, DoD Instruction (DoDI) 3216.02 outlines additional requirements and guidance for research conducted involving DoD-affiliated personnel. This instruction document defines DoD-affiliated personnel as service members, reserve service members, National Guard members, DoD civilians, and DoD contractors.

Per DoDI 3216.02(3.9)(f)(3), military and civilian supervisors, officers, and others in the chain of command are prohibited from influencing their subordinates to enroll in human participant research. Subsection (4) requires these individuals not be present during recruitment sessions or the consent process. If potential participants are approached in a group setting, this means their superior officers should not be present.

For minimal risk research, an alternative consent process may be appropriate. For example, in a survey study for which results are aggregated and linking to individual participants is not required for data analysis, informed consent could be obtained from the participant via an electronic platform during a time when he or she is not on duty. If necessary, participants can contact members of the study team with any questions they have before consenting.

For more than minimal risk research where recruitment is conducted in a group setting, the DoDI outlines additional protections. The IRB must appoint an independent ombudsperson to supervise the recruitment activity and consenting process. This person should explain to participants that their involvement is voluntary. They should also ensure the IRB-approved recruitment script, digital materials, and consenting process are followed (DoDI 3216.02(3.9)(f)(6)(b)).

Members of the study team should identify themselves and their relationship to the DoD as part of the recruitment and consenting process. Participants should be informed of the extent to which the research records may be accessible by the military. If the research is covered by a Certificate of Confidentiality, the consent form should explain the scope of this protection along with any exceptions that may limit it.

Compensation of DoD-affiliated personnel while on duty is prohibited, with some limited exceptions defined by statute (DoDI 3216.02(3.9)(f)(7)). As such, study team members should be aware of what they can and cannot offer as compensation to these participants.

Elderly Patients in Group Healthcare Settings

The biggest area of concern for elderly participants who reside in a residential healthcare facility is their decisional capacity or ability to consent for themselves. Elderly patients may have reduced mental capacity that is temporary, progressive, or permanent due to any of the

following: ongoing disease processes, acute urinary tract infections, neurological disorders like stroke or dementia, psychoactive medications, head trauma, or even past substance abuse. This means evaluation of an elderly patient's mental capacity is an essential step in any consenting process and should be an ongoing consideration throughout the duration of a research study.

The regulations do not direct specific requirements for consenting participants with reduced mental capacity, but they do identify individuals with impaired decision-making capacity as likely to be vulnerable to coercion or undue influence (45 CFR 46.111(b)). As such, the study design should incorporate additional protections for these participants. The research procedures should involve regularly assessing the participant's capacity throughout the study and obtaining consent with the help of the participant's legally authorized representative (LAR).

Even if the planned research is short in duration and a potential participant is otherwise decisional, it is advisable to involve an LAR or family member in the process. An otherwise alert and decisional elderly patient may not feel comfortable asking questions or voicing his or her objections in this setting. The participant's LAR or family member can serve as an advocate during the consenting process to voice any concerns or objections, if needed.

For research that presents more than minimal risk, the study team should plan for a longer consent process by conducting the discussion over multiple visits. This will provide the potential participant and his or her LAR with a chance to review the consent form in detail and formulate any questions they may have for the study team. This will also let the elderly patient discuss participation with the LAR privately. Because patients have an ongoing relationship with the care facility where they stay, they may be reluctant to refuse to participate for fear of upsetting their caregivers or the study team members who may also be providing them with clinical care. Extending the consent process to give the patient and LAR time to discuss their concerns reduces this feeling of pressure to participate.

For longitudinal studies that follow the progression of disease resulting in reduced capacity, it is advisable to have the participant's LAR identified ahead of time even if he or she is not needed during the initial consenting. This is especially important if the disease progresses and the formerly decisional participant is no longer able to adequately evaluate his or her own needs and

interests. Some progressive conditions have good days and bad days, and a participant's capacity may vary along a spectrum. An LAR who is familiar with the participant's personality and medical history will be able to step in for the participant to evaluate continued participation when necessary.

Students

Although students are not granted additional protections by the regulations, [they can still be considered vulnerable](#) by virtue of their concern for their own academic well-being and the power differential between them and the study team working with their professor. As such, study team members should adopt the following best practices to reduce the pressure to enroll that these potential participants may feel.

The study team should not include the student's professor as a member, since potential participants may be concerned that they will receive a bad grade or other punishment if they do not agree to enroll in the research. If this situation cannot be avoided, the study team should arrange to have someone other than the professor obtain consent from participants. Ideally, the professor should not be present during the recruitment and consenting activities.

If possible, the study team should design the protocol in such a way that the professor will not know who participates and who does not. For example, recruitment for research involving an anonymous survey could take place in person, but the study team could request a waiver of documentation of consent so participants will not have to provide their names on forms linking them to their participation.

For research that offers extra credit as compensation for participation, the study team should arrange to have an alternative option available to students who do not wish to participate, as some students may feel pressured to enroll in research that they would otherwise avoid to obtain the extra credit they need to get a good grade. This alternative option should involve a similar time commitment and level of effort—for example, a research survey that takes an hour to complete could be presented alongside an assignment that takes about the same amount of time.

Ideally, there should be protections in place to anonymize which students participated in the research and which students opted to complete the extra credit assignment instead. These protections should be clearly communicated to the potential participants as part of the consent process.

In addition to perceived pressure from the study team, students may also experience peer pressure to enroll (or not enroll), depending on their age. If this is a concern, study team members should conduct the consent process privately rather than in a group setting. Team members could also consider asking the students to not discuss their participation with each other until after the research activities are completed.

Conclusion

When conducting research in participant populations that are more susceptible to feeling pressure to participate, study teams need to be mindful of regulatory requirements and adopt a consent process that minimizes this pressure. Depending on the circumstances, this may require additional consent disclosures, identifying different individuals to conduct recruitment and obtain consent, changing the consenting setting, relying on the participation of an LAR, or designing the research procedures to limit who on the study team knows who participated. A well-developed consenting process will reduce a participant's perceived pressure to enroll in the study.



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PRESCRIPTIONS FOR BUSINESS

Patient-First Strategy vs. “Pharma Strategy Expertise” for Building Clinical Research Success in Rare and Orphan Disease Treatment

Donvan Quill



Rare diseases affect 1% or less of the global population, with the geographic spread and small number of those impacted making [the cost of research and development](#) (R&D) prohibitive and leaving patients without treatments. Of the 7,000 known rare diseases, [95%](#) thus far do not have a single drug treatment approved by the U.S. Food and Drug Administration (FDA).

Historically, rare diseases have not attracted significant pharmaceutical investment; today, however, that is changing. In fact, large pharmaceutical companies have begun to focus on rare diseases, drawn by government incentives and the growing likelihood that treatments for what are often life-threatening or severely debilitating diseases will be successful.

About [33%](#) of all drugs in active R&D pipelines are now included in the rare disease category, presenting scientific and operational challenges to sponsors and clinical trial ecosystem participants, as well as spurring the adoption of new strategies, operating models, and processes.

Clinical research professionals seeking to build a go-to market strategy, however, may feel overwhelmed about where to start and may be tempted to revert to a so-called “pharma strategy expert.” This term is misleading, given that it’s impossible to provide expertise across the wide range of therapies for rare and orphan conditions. Each patient is unique in terms of the treatment, points of care, physicians, and level of caregiving they require.

Self-appointed rare condition experts may be virtuosos in big pharma or skillful in commercialization strategies with a particular condition, but too often they fall far short of expectations. They offer an ever-increasingly complicated process that fails to be cost effective. What's more, cookie-cutter pharma strategies have no place in today's complex and ever-evolving healthcare environment. What's needed is a patient-first approach that relies on a team of experts who bring a specific understanding to *each patient's condition* to provide effective therapy and care management.

The Downside of Rare Disease Experts

Rare disease “experts” begin with inherent assumptions about care delivery and optimization to map the patient journey. They attempt to break down a strategy into multiple phases, such as precommercial planning and distribution. All of this can be justified with outmoded approaches to care and may sound rational. The problem is that each new phase of the process contains hidden costs and growing complexity with the creation of layers between the clinician and patient that often fail to improve patient outcomes.

In fact, this approach can become so complicated that pharma execs must pay for additional management staff to oversee the process and inform the clinician about next steps in patient services. This not only adds costs and unnecessary layers between the patient and clinician, but also obscures data and outcomes.

When optimizing care for rare and orphan disease patients, the best place to begin is at the end: the patients who require therapy. It's important for stakeholders to learn their individual needs and expectations. They must also understand that compassion—and not managerial layers—is vital for patient quality of life and improved outcomes.

With a patient-first strategy, pharmaceutical manufacturers and their clinical research professionals can build a commercialization team that is open, curious, and empathetic. Patient-first strategies offer targeted programs and services that deliver specialized expertise that transcends the scope of capabilities provided by traditional, legacy care organizations, which are often designed exclusively for scale.

A Patient-First Strategy Mitigates Clinical Trial Disruption

A patient-first approach provides comprehensive, best-in-class services tailored to maximize therapeutic opportunities for people in the rare disease community, including counseling, guidance, and education based upon patient and caregiver needs.

The benefits of partnering with a specialty pharmacy and patient management organization that takes a patient-first approach have been put in bold relief during the COVID-19 pandemic. The best of these organizations use tools to enable in-home clinical services, direct-to-patient support, and remote monitoring for keeping clinical trials on track. This approach can significantly shorten the time from the clinical trial to commercial drug access.

The pandemic represents additional issues facing patients, researchers, providers, and drug manufacturers in the rare and orphan disease market. These challenges include the high cost of clinical trials and patient recruitment. While traditional models are built for scale, a patient-first approach focuses on and customizes services for small patient populations, delivering expertise to overcome the limitations of legacy care models and providing cost-effective programs. This streamlined approach includes financial advantages, assurance that products are properly and promptly distributed, and patient services designed to ensure compliance and quick, accurate reimbursement processing.

Further, integrated telehealth features have enabled patients to get the products delivered without going to the doctor's office. As a result, the trials conducted during the pandemic had significantly more patients involved, despite the national lockdown. This approach helps to build awareness and introduce education programs that aid understanding of patient groups, and clinical research professionals and manufacturers know they have the support to develop a drug and a comprehensive program based upon specific needs.

High Level Support for Specialty Patients

The higher level of care continuity delivered by a patient-first approach strengthens communication, yields rich data for more informed decision making, and improves the overall patient experience. Dedicated clinical teams are better able to seamlessly eliminate treatment

gaps for the patient. This strategy also addresses all variables around collecting data, while maintaining frequent communication with patients and their families to ensure compliance and positive outcomes.

A patient-first care team that includes care coordinators, pharmacists, nurses, and other specialists focuses on the disease state, patient community, and therapy. This is critical for transcending the limitations of the standard specialty pharmacy and hub service provider, which too often rely on technology solutions that fail to address human needs and variability.

Finding the Right Patient Management Partner

When identifying a specialty pharmacy and patient management organization that creates a partnership for personalized care, look for a partner that offers a suite of comprehensive services tailored to maximize the therapeutic opportunities for the treatment of rare and orphan disorders. A patient-first approach can provide the trusted path for patients and all those involved in the treatment journey. This adds much-needed support for the patient's family and caregivers, enabling them to become more engaged and take ownership, which leads to a stronger partnership and better patient care.

Telehealth Considerations

The partner's telehealth solution should be designed to streamline patient enrollment, maximize interaction with patients for adherence and compliance, and provide continuity of care to avoid lapses in therapy. It should rely upon dedicated team members who have expertise in every aspect of the patient's drug and can address every question and concern from patients, pharmacists, physicians, providers, and payers.

Effective telehealth is particularly important for addressing the unique healthcare coordination needs of patients with a rare or orphan disease and, more importantly, the newly diagnosed patient.

As part of a larger personalized care plan, and tied specifically to a particular specialty drug, telehealth enables pharmacists to empower their patients to thrive, even during times of

disruption and uncertainty brought on by the COVID-19 pandemic and other unforeseen emergencies.

Customized care coordination and telehealth solutions add another layer to a proactive, process-driven program, educating the patient on potential risks. This fosters discussion between the patient and providers that is essential to understanding the patient's needs, providing focus on the drug's impact and monitoring overall health. By incorporating assessments and predetermined touch points each month, the care team is able to stay on top of side effects and capture real-world evidence around the therapy, the disorder, and the person's well-being.

Closing Thoughts

On top of everything else already mentioned, the most effective specialty partner should demonstrate expertise in navigating the insurance landscape and prior authorization process, as needed, and know how to monitor and encourage compliance. It's also important to find a partner with dual accreditation from the Utilization Review Accreditation Commission (URAC) for compliance with specialty pharmacy and the Accreditation Commission for Health Care (ACHC) for specialty pharmacy services. This demonstrates commitment to providing quality care and services to these patient populations.

Ideally, the care management solution should meet the needs of everyone involved in the patient's journey, from clinical research professionals and specialty drug manufacturers to pharmacists, caregivers, and physicians.



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Informed Consent: Opening New Doors

Article #1: Consent Process Best Practices for Special Populations to Reduce Perceived Pressure to Participate in Clinical Trials

LEARNING OBJECTIVE

After reading this article, the participant should be able to distinguish between coercion and undue influence in terms of clinical research participation, identify populations that may be at risk of such practices, and outline steps to be taken in addressing related concerns.

DISCLOSURES

Sean Horkheimer, JD, CIP: *Nothing to disclose*

- 1. Threatening to withhold medical care from someone unless they participated in a clinical trial would be an example of which of the following?**
 - a. Undue influence
 - b. Bribery
 - c. Coercion
 - d. Larceny

- 2. Additional requirements are placed upon study teams and institutional review boards (IRBs) to protect which of the following from instances of coercion to join trials?**
 - a. Healthcare workers and first responders
 - b. Elderly patients and their caregivers
 - c. Students and members of religious orders
 - d. Military personnel and prisoners

- 3. Which of the following would be considered an example of undue influence over a prisoner being asked to join a trial?**
 - a. Implied threats of harm against his or her family for not participating.
 - b. Offering him or her a larger cell and better food for participating.
 - c. Promising to lengthen his or her sentence for not participating.
 - d. Refusing to allow him or her visitors until participation is agreed upon.

- 4. What does the author recommend members of a study team should do when consenting a prisoner for a trial?**
 - a. Identify themselves and their relationship to the prison.
 - b. Consent all prisoners at the same time for security reasons.
 - c. Remain anonymous to the prisoner throughout the process.
 - d. Only conduct the process remotely whenever possible.

5. A Department of Defense Instruction prohibits which of the following from influencing military personnel to enroll in human participant research?

- a. Municipal authorities in areas where military bases are located.
- b. Federally contracted vendors doing business with the military.
- c. Healthcare officials or consultants visiting military facilities for any reason.
- d. Anyone above the potential participant in the chain of command.

6. Which of the following is an extra protection an IRB must provide in more than minimal risk research in military settings?

- a. The guarantee of assignment to a placebo group if demanded as a condition of participation.
- b. The arrangement of special duties and other accommodations in case of serious adverse effects.
- c. The appointment of an ombudsperson overseeing participant recruitment and consenting.
- d. The confirmation that the participants have no families or legally recognized dependents.

7. What do the regulations say about evaluation of an elderly patient's mental capacity in relation to participation in research?

- a. It is of negligible importance if a legally authorized representative feels an impaired patient would have participated in normal circumstances.
- b. It is important because individuals with impaired decision-making capacity may be vulnerable to coercion or undue influence.
- c. It is only of importance to regulators if any participants with reduced capacity are located in countries outside the United States.
- d. It is of no importance if a participant's mental capacity changes during the course of the study for better or worse.

8. The author advises which of the following regarding legally authorized representatives (LARs) for elderly participants in studies tracking progression of a disease that affects mental capacity?

- a. LARs should be identified ahead of time even if capacity is not an issue during consent.
- b. LARs have no role to play in the consenting of participants with sufficient mental capacity.
- c. LARs should only become involved if a participant becomes mental incapacitated during a study.
- d. LARs are to be considered the sole judges of an elderly patient's mental capacity.

9. Which of the following does the author recommend regarding participation by students in research led by one of their professors?

- a. The professor should identify the best candidate students for participation based on their grades and classroom enthusiasm.
- b. The university should prohibit professors from including students in their research except for those from other institutions.
- c. Professors should not be made aware of which students participated in their study until it is time to assign grades for the course.
- d. The study team should design the protocol such that the professor cannot identify participants versus non-participants.

- 10. The author recommends which of the following in cases where students do not wish to participate in research in exchange for extra credit?**
- Allowing the students to participate in some other professor's research for the same reward.
 - Penalizing the students for not cooperating with the professor's pursuit of research.
 - Offering the students an alternative option for gaining credit requiring similar time and effort.
 - Encouraging the students to find peers from other classes to take their place in the study.

Article #2: Patient-First Strategy vs. "Pharma Strategy Expertise" for Building Clinical Research Success in Rare and Orphan Disease Treatment

LEARNING OBJECTIVE

After reading this article, the participant should be able to summarize the application of patient-first strategies to rare and orphan disease treatment and factors that limit the abilities of standard pharmaceutical industry approaches to address this area more thoroughly.

DISCLOSURE

Donovan Quill: *Nothing to disclose*

- 11. Which of the following factors is cited by the author as a reason large pharmaceutical companies are focusing on rare diseases?**
- Central IRBs are more likely to approve proposed clinical trials for many rare diseases.
 - The availability of government incentives and promising trends for successful treatments.
 - Regulators are willing to waive most inclusion/exclusion criteria for rare disease patients.
 - Successful treatments for rare diseases can often be repurposed for more common conditions.
- 12. Why does the author say the term "pharma strategy expert" is misleading?**
- There are no accredited academic programs providing instruction in pharmaceutical development strategies.
 - Research and development expertise gained in other industries is not transferrable to pharmaceutical companies.
 - A patient's unique characteristics make it impossible to be an expert across all therapies for rare and orphan conditions.
 - There are no widely agreed-upon definitions for rare and orphan conditions to support their study by clinical researchers.
- 13. Which of the following is cited by the author as contributing to failures to improve patient outcomes through research and development projects for rare disease treatments?**
- Hidden costs and growing complexity in the process add layers between clinicians and patients.
 - Rare disease patients are increasingly unlikely to remain in studies through their completion.
 - Excessive changes to ongoing study protocols in rare disease situations preclude most breakthroughs.
 - Sponsors of rare disease studies rarely allow them to continue long enough to deliver actionable data.

14. The author cites which of the following as being vital to quality of life and improved outcomes when caring for rare and orphan disease patients?

- a. Efficacy
- b. Compliance
- c. Data management
- d. Compassion

15. Which of the following is cited as a feature of a patient-first approach when conducting a clinical trial?

- a. Allowance for participants to obtain treatment products from their preferred source.
- b. Customization of services for small patient populations in recruitment and trials.
- c. Encouragement to investigators to treat participants in more off-label situations.
- d. Validation of all patient-reported outcomes through independent research teams.

16. Higher levels of care continuity in patient-first approach situations are said to lead to which of the following?

- a. Better marketing of resulting treatments
- b. Higher likelihood of regulatory approval
- c. Stronger communication
- d. Lower costs for study sites

17. Which of the following is cited as a shortcoming of specialty pharmacy and hub service providers?

- a. Refusal to be involved in studies of rare and orphan diseases.
- b. Unlikely to be approved for use through central IRB processes.
- c. Lengthy contracting and billing procedures leading to delays.
- d. Reliance on technology solutions that are insufficient for the task.

18. In rare disease studies, a patient management partner's telehealth solution should be able to do which of the following?

- a. Minimize adverse events
- b. Streamline enrollment
- c. Maximize dosing
- d. Identify professional patients

19. The author cites which of the following as helping educate patients about the potential risks of participating in a trial?

- a. Customized care coordination
- b. Study protocol
- c. IRB mid-study review
- d. Clinical research associate

20. How can a provider of specialty pharmacy services demonstrate commitment to its involvement with rare and orphan disease patient populations?

- a. Obtaining authorization from multiple patient advocacy groups.
- b. Sponsoring recruitment drives to attract patients to new studies.
- c. Holding accreditation from two commissions devoted to such services.
- d. Supplying approved treatments for rare conditions at discount rates.