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WHITE PAPER

MINIMIZING IRB RESUBMISSIONS TO MAXIMIZE CLINICAL TRIAL ENROLLMENT

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Regulatory resubmissions cost both money and time, and can significantly delay patient enrollment for a clinical trial. This comprehensive paper explores common reasons for resubmissions as well as potential resolutions, with insights from the following regulatory and patient recruitment experts:

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Vice President, Operations, DAC Patient Recruitment Services

DAVID HOLT
Vice Chair, Regulatory, Western IRB

STEPHEN TODD,
Manager Client Support, Quorum Review IRB

INTRODUCTION

Biopharmaceutical companies and CROs face a challenging clinical development landscape—one in which opportunities seem boundless yet demands are immense. To put things in perspective, more than 80 percent of trials miss patient enrollment deadlines resulting in delays that can cost upwards of $8 million daily.[1] Additionally, the clinical research industry has experienced double-digit annual growth in recent years, prompting unprecedented competition.[2] All things considered, anything that contributes to enrollment delays must be critically evaluated. This includes resubmission of trial protocols and patient materials to the institutional review board (IRB).

IRBs – and ethics committees (ECs) in non-U.S. countries – ensure that appropriate safeguards exist to protect the rights and welfare of human research subjects. Though their sovereignty to review protocols and patient materials is not explicitly expressed in federal regulations, it is implied in 12 CFR 56.109 and 45 CFR 46.109, which reads that the Food and Drug Administration and Office for Human Research Protections give the IRB "authority to approve, require modifications in, or disapprove all research activities" covered by the regulations.[3]

Sources say IRB-requested protocol revisions are frequently due to inadequate protocol planning, factual inaccuracies and lack of detail. Conversely, IRB modifications to recruitment materials are usually aimed at correcting language that promotes therapeutic misconception among study participants.

This white paper explores common reasons and possible resolutions for IRB resubmissions in each category – protocols and patient materials – as seen by regulatory and patient recruitment experts.

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COUNTING THE COSTS

According to Melynda Geurts, vice president of operations at DAC Patient Recruitment Services, regulatory resubmissions are expensive in more ways than one.

SPONSOR-GENERATED PROTOCOL AMENDMENTS AVERAGE $1 MILLION.

In terms of dollars, she estimates: "It varies from $150 to $250 per piece to be reviewed. Some costs are per site as well. If recruitment materials are submitted with the protocol, it falls under the protocol review cost, which is about $1,500. So it's added cost or could be seen as scope creep that isn't necessarily planned for."

In terms of delays, she adds: "Most IRBs will do a 48-hour expedited review, but you do have some that take between five to 10 business days even for resubmission. This doesn't take into account local IRB timelines, which can push things out by a month."

Proactive planning is essential, she says, considering that recruitment costs $1,500 to $10,000 per patient, sponsor-generated protocol amendments average $1 million, and timeline extensions range from $1 million to $8 million per day.

FIRST THINGS FIRST: STUDY DESIGN

Without question, the protocol is a pivotal document in clinical trial planning. Yet growing protocol complexity has come under fire in recent years for its correlation with longer study cycle times, poorer patient recruitment and retention rates, and a higher number of protocol amendments. As a result, clinical trial sponsors are challenged to evaluate protocol complexity in comparison to competing studies and within the context of study objectives, endpoints and procedures. But according to regulatory sources, the quest for streamlined design in addition to investigator inexperience, may contribute to protocol rejection or deferred approval.

OFTENTIMES, SPONSORS DON'T THINK ABOUT RECRUITMENT AND/OR RETENTION CHALLENGES DURING THE PROTOCOL DESIGN/DEVELOPMENT PHASE BUT THEY SHOULD.

"Protocol quality is key, but we see a lot that are sparse – even lacking inclusion and exclusion criteria," says David Holt, vice chair of Regulatory at Western IRB (WIRB). "They may describe what the investigator wants to do, but not how they're going to do it, namely, how they're going to recruit research subjects. This is particularly common among protocols submitted by inexperienced investigators and those who are sponsoring the studies themselves."

Geurts agrees that recruitment and retention planning should start at the point of protocol design but, too often, they are afterthoughts, which can profoundly impact budgets and timelines.

"Protocol design determines the accessibility of the target population," she says. "Oftentimes, sponsors don't think about recruitment and/or retention challenges during

the protocol design/development phase but they should. Considering potential enrollment and attrition obstacles could limit the need for protocol amendments and/or addition of more sites because enrollment targets are significantly lagging or attrition is rising to an alarming level."

Stephen Todd, manager of Client Support at Quorum Review IRB, says rejection or deferred approval of a protocol typically occurs when the research lacks background, scientific justification, or clear procedures or endpoints. "If the issues with the study are minor and just require clarifications, Quorum will typically postpone consideration of the study and send an inquiry to the researcher or sponsor/CRO, as applicable," he explains.

ICH Good Clinical Practice Guidelines (Section 6) require that protocols include the following general content, though some of this may be featured in other reference documents, such as the investigator's brochure:[4]

- General Information
- Background Information
- Trial Objectives and Purpose
- Trial Design
- Selection and Withdrawal of Subjects
- Treatment of Subjects
- Assessment of Efficacy
- Assessment of Safety
- Statistics
- Direct Access to Source Date/Documents
- Quality Control and Quality Assurance
- Ethics
- Data Handling and Recordkeeping
- Financing and Insurance
- Publication Policy
- Supplements

Holt says WIRB reviews protocols against a detailed checklist, such as the above, with an emphasis on risk and benefits analysis.

"Developing a protocol for a big drug or device trial takes months, while a protocol for a much smaller trial may only take days to develop. There is a huge variation," he notes. "The big drug and device trials take a lot of effort, and the protocols get revised a lot by the sponsor. In fact, we may see revisions coming in every month for one protocol. We have to review each revision with the same meticulous attention to detail. Objective scientific outcomes with value are important."

PERSPECTIVES ON PATIENT RECRUITMENT MATERIALS

Every clinical trial needs a voice – messaging that communicates the trial sponsor's core objectives. Patient recruitment professionals provide this through compelling content and artful designs that resonate with target audiences and inspire study participation. But beyond being current and compelling, study collateral must also be regulatory-compliant.

Though regulations vary slightly per country, generally speaking, patient-facing content that promotes an investigational product must make no expressed or implied claims of

"There should be no overly positive statements or smiling faces, and no hard-selling of compensation."

efficacy according to the Code of Federal Regulations Title 21, Sec. 312.7, Promotion of investigational drugs. That sounds simple enough, but the term "implied" is subjective and open to interpretation. So what is a site or patient recruitment strategist to do?

"Err on the side of caution," Holt quips.

Of the 500 to 1,000 submissions received at WIRB weekly, deferrals and rejections are most often due to poor protocol planning and promissory patient content, Holt says, adding:

"We frequently reject materials that are overly reassuring. For example, we might see an ad for a new product or device that claims to be efficacious or a possible cure. Use of the word treatment is not necessarily a deal-breaker. It depends on the context; we have no blanket rule regarding use of the word. But to make precipitous claims of efficacy is something we want to avoid. We don't want a subject to be misled into enrolling in a trial based on false claims. We also don't want undue emphasis on compensation."

An essential first step in compliance is knowing what materials must be submitted to regulatory. Below is a breakdown of what is, and is not, within the IRB's purview:[5]

WHAT REQUIRES IRB REVIEW?

- Direct advertising (print, broadcast, digital, billboard advertising)
- The content and the mode of communication, as well as the final copy and format

WHAT DOES NOT REQUIRE IRB REVIEW?

- Communications intended to be seen or heard by health professionals
- News stories (unless intended to recruit subjects)
- Publicity intended for other audiences, such as financial page ads geared toward prospective investors
- Listings of clinical trials on the Internet when limited to basic trial information (i.e., title, study purpose, protocol summary, basic eligibility criteria, study site location)

Todd of Quorum says his institution evaluates both the content of advertisements as well as the mode of communication, with the following questions in mind:

1. Is this direct advertising or a clinical trial listing that allows additional descriptive information about the trial?
2. Is the proposed plan for recruiting or advertising (including the information provided and mode of communication) coercive, or does it represent a risk to privacy or confidentiality of participants?
3. Does the information provided imply a favorable outcome beyond what should be expected of the research?
4. If the study involves investigational products, does the advertisement claim that a study product is safe, effective, equivalent, or superior to other products?
5. If payment is mentioned, is the payment or the amount of payment over-emphasized?
6. Does the advertisement use phrases, such as "free medical treatment" when intending to describe study procedures or receiving the study product?

"Given the FDA's interpretation that advertisements are the beginning of the informed consent process, Quorum Review IRB reviews recruitment materials to ensure that participant selection is equitable and that advertising materials abide by important informed consent principles," Todd explains. "Advertisements must not contain exculpatory language, unduly coercive or misleading content, or promise of a cure beyond what is outlined in the consent.

Asked to provide specific reasons Quorum might reject a submission or defer approval, he says, "to remove an emphasis that payment is being provided for participation, or to remove information that implies the use of an investigational product should be considered medical treatment and could contribute to therapeutic misconception."

Therapeutic misconception – the bane of informed consent since the inception of clinical research – occurs when a patient misunderstands the purpose of the research or believes medical research to be synonymous with medical care. To avoid this, Todd says advertising materials must clearly communicate that research is aimed primarily at gathering knowledge and may not provide any therapeutic benefit.

"There should be no overly positive statements or smiling faces, and no hard-selling of compensation," Holt offers. "Even if an investigational drug has shown efficacy for another indication, or is currently approved and marketed for other indications, that should not be mentioned because it is considered coercive."

To assist sponsors and sites many IRBs publish guidelines for developing patient materials. Though the granular details vary between documents, the listings below represent the general recurring theme:

REQUIRED PATIENT CONTENT

- A statement indicating a research study is being conducted
- The disease or condition being studied
- Key eligibility criteria in layman's language, for example, liver instead of hepatic, heart instead of coronary, etc.
- Contact information so potential participants can request more information

ADDITIONAL PERMITTED PATIENT CONTENT

- The purpose of the research
- The location of the research
- The company sponsoring the research (if the client agrees to include this)
- Whether the participant will be compensated for participation
- Balanced statements of potential benefits and risks of study participation

PROHIBITED CONTENT

- Claims of safety or effectiveness
- References to "free medical treatment" when the intent is only to say participants will not have to pay for taking part in the study
- Undue emphasis on patient reimbursement by giving the dollar amount or through special text treatment, such as boldface, italics or underlining
- Claims that the investigational product is approved by the FDA or other regulatory body for use in patients with the target disease or condition
- Use of the term "new" unless qualified as a "new investigational medication"
- Use of the term "treatment" in the context of the investigational medication
- The compound name, unless it is currently approved and marketed for another indication and the sponsor approves of its use in the materials
- Overly promotional terms such as groundbreaking, exciting, important, unprecedented, etc.

GRAPHIC REQUIREMENTS

To avoid subliminal implications of efficacy, avoid depictions of smiling faces or people who appear markedly healthier than the target population. For example, an advertisement aimed at patients with mobility issues should not feature images of people performing physically demanding feats, such as mountain-climbing.

"From the protocol to the patient advertisements, accuracy and objectivity are paramount," Holt concludes. "The protection of research subjects is a serious matter, and one that every individual involved in the clinical trial process should consider in all that they do."

[1] Center for Information & Study on Clinical Research Participation.

[2] PAREXEL's Bio/Pharma R&D Statistical Sourcebook

[3] Code of Federal Regulations. ICH Guidelines. 12 CFR 56.109 and 45 CFR 46.109.

[4] ICH Good Clinical Practice Guidelines, Section 6: Clinical Trial Protocol and Protocol Amendment(s).

[5] U.S. Food and Drug Administration. Recruiting Study Subjects - Information Sheet. Guidance for Institutional Review Boards and Clinical Investigators.

ABOUT THE AUTHOR

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Felicia leads brand messaging and content development for DAC's corporate and client collateral, including print and digital material targeted to patients and clinicians. She is a widely published writer with 24 years of journalism and corporate communications experience, including eight years with DAC. Her writing talents have garnered 13 awards, including four International Hermes Awards and four International AVA Awards since 2010, alone. Felicia was a contributing writer and editor for two industry books: "Global Issues in Patient Recruitment and Retention," and "International Patient Recruitment Regulatory Guidelines, Customs and Practices."