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Human Research Report™

PROTECTING RESEARCH SUBJECTS AND RESEARCHERS

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IRBs and Special Ethical Issues in Investigational New Drug Studies (#1)

This month's lead article on an FDA guidance is unusual in that it involves a relatively rare set of conditions and the associated research paradigms that apply.

However, what is singularly important for many IRBs is that the primary ethical and regulatory issues that apply in this case are ones that can cause major IRB review challenges in any kind of clinical study.

Hence, this article will focus on those particular IRB topics.

For those IRBs and researchers who are active in the field of oligonucleotide drug research, we will present practical tips and advice from the new FDA guidance for such researchers in future HRRs.

For now, we will leave the more detailed explanations contained in the FDA recommendations for said researchers to examine on their own.

Even if this particular research field is not relevant for IRBs or researchers, the guidance's tips on how to most successfully interact with FDA staff most certainly are relevant.

The emphasis in this guidance is on very early studies and recommended best ways to seek the FDA's guidance. Correctly doing so should minimize roadblocks in seeking subsequent FDA approval of a new drug product.

Protection of Human Research Subjects Remains a Top Priority

The newly released draft guidance is titled "IND Submissions for Individualized Antisense Oligonucleotide [ASO] Drug Products: Administrative and Procedural Recommendations."

ASOs are defined as "... small-sized single-stranded nucleic acids ... [that can often] offer some advantage over 'siRNAs' in terms of targeting both nuclear and cytoplasmic located 'lncRNAs.' Based on their sequence homology, ASOs bind to their target RNA sequence inside the cells and bring about gene silencing ....

ASO drugs are also being investigated to be used in combination with nanoparticles" (See M. Kumar, et al., *Molecular and Cellular Changes in the Cancer Cell*, in the book titled PROGRESS IN MOLECULAR BIOLOGY AND TRANSLATIONAL SCIENCE, 2016).

NOTE #1: Quoted materials in this newsletter appear exactly as originally published in source documents, including any misspellings, grammatical errors, missing words, etc. However, we will on occasion insert words in brackets [ ] to make the material easier to read, to edit text or formatting, or to add an editorial comment.

NOTE #2: Emphases are added to articles by HRR by underlining or adding ***bold/italics*** to selected text, unless stated otherwise.

NOTE #3: Articles **T**o **B**e **C**ontinued **{TBC}** in subsequent issues are marked at the end with **{TBC}**.

ALSO IN THIS ISSUE

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"This draft guidance is intended to help sponsors developing individualized ASO drug products for a severely debilitating or life-threatening genetic disease.

The draft guidance addresses the approach for obtaining feedback from FDA, the expectations and process for making regulatory submissions to FDA, and high-level recommendations related to the requirement for institutional review board review of protocols for trials of individualized ASO drug products and the informed consent of participants.

The draft guidance discusses the importance of early interaction with FDA, submission expectations for pre-investigational new drug (INDs) meeting packages and IND applications, and ethical and human subject protection considerations ....

The draft guidance is expected to facilitate the preparation of adequate pre-INDs and IND submissions for review by the Agency, which may help enable prompt initiation of the investigation" (86 Fed. Reg. 314-315 at p. 315, January 5).

IRBs Must Be Notified By Researchers Very Early in the Clinical Trial Process

"This draft guidance represents the first of several guidances FDA intends to publish to advise and help sponsors developing individualized ASO drug products for patients who have severely debilitating or life-threatening diseases or conditions and no adequate alternative therapy available to them to treat their disease or condition" (ibid).

The primary portion of the guidance that specifically addresses IRB-related issues is titled "**D. Ethical and Human Subject Protection Considerations**." In part, that section states that:

"Because of the nontraditional nature of drug development in this arena, complex ethical issues may arise. As such, sponsors should consider conferring with a medical ethicist when developing their protocol.

1. IRB Review

Under FDA regulations, a protocol under which an individualized ASO drug product is administered to a human subject must be reviewed by an IRB (21 CFR Part 56), which must fully evaluate the protocol and ensure that risks to the subject are reasonable in relation to the anticipated benefits (21 CFR 56.111(a)(2)).

The IRB should be provided with the results of all relevant nonclinical safety studies in animals that have been conducted. Sponsors should consider contacting their IRB as early as possible.

If the ASO drug product will be administered to a child, the IRB must ensure that the protocol complies with the requirements under 21 CFR part 50, subpart D" (guidance, January, at p. 8; on the Web at https://www.fda.gov/media/144872/download).

Some Risks to Human Subjects May Be Unknown Prior to Study

"*2. Informed Consent*

Under FDA regulations, informed consent must be obtained under circumstances that provide prospective participants, or their legally authorized representatives, sufficient opportunity to consider whether to participate and that minimize the possibility of coercion or undue influence (21 CFR 50.20) ....

The informed consent document and the consent discussion should appropriately emphasize in a clear manner that the ASO drug product is experimental, the reality that the benefit is uncertain and the potential risks are unknown, and that additional costs to the participant may be associated with the administration of the drug product.

When appropriate, the consent document and consent discussion should include information that the administration of the ASO drug product will be the first use in humans of the investigational drug and relevant information from nonclinical safety studies in animals that have been conducted that could potentially inform the safety of the participant" (ibid). © **{TBC}**