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PROTECTING RESEARCH SUBJECTS AND RESEARCHERS

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IRBs and Human Gene Therapy for Neurodegenerative Diseases (#1)

In the March HRR we described a new FDA guidance for which the agency was seeking public comments until April 6. That guidance, which we feature now, is titled "Human Gene Therapy [HGT] for Neurodegenerative Diseases."

In addition to continuing to be a cutting-edge medical science field, HGT research is at the heart of the new vaccines created to combat COVID-19.

Aside from its ramifications for the ongoing pandemic, HGT poses special considerations for IRBs and researchers, regardless of the intent of any particular HGT study. For example, as we shall discuss later, there are particular risks in HGT for any human subjects involved. Subject enrollment and retention also offer special considerations.

> "This guidance focuses on considerations for product development, preclinical testing, and clinical trial design" (86 Fed. Reg. 549, January 6).

Guidance Is for Both Pediatric And Adult Human Subjects

The guidance notes that it is designed to address specific issues in HGT involving both pediatric and adult human subjects.

> "This guidance provides recommendations to sponsors developing human gene therapy (GT) products[1] for neurodegenerative diseases affecting adult and pediatric patients.
>
> (FN #1: Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use.
>
> FDA generally considers human gene that mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences.

Some examples of gene therapy products include nucleic acids (e.g., plasmids, in vitro transcribed ribonucleic acid (RNA)), genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing, and ex vivo genetically modified human cells ….).

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 **To Be Continued {TBC}** in subsequent issues are marked at the end with **{TBC}**.

Also In This Issue

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Neurodegenerative diseases are a heterogeneous group of disorders characterized by progressive degeneration of the structure and function of the central nervous system or peripheral nervous system.

These diseases vary in etiology, prevalence, diagnosis, and management, and include genetic as well as age-related diseases" (guidance, January, p. 1; on the Web at https://www.fda.gov/media/144886/download).

Focus Is On Clinical Trials

There are several pages of the guidance which we shall skip. Those sections address various manufacturing and preclinical study issues.

While the portions of those areas that can later affect subject safety certainly warrant attention from relevant researchers (e.g., dosage strength, purity, interactions, etc.), we shall focus on the section titled "IV. Considerations for Clinical Trials."

"The fundamental considerations for clinical development programs of GT products for neurodegenerative diseases are similar to those considerations for other biological products, as detailed in [other] relevant FDA guidance documents ….

FDA recognizes that neurodegenerative diseases constitute a heterogeneous group of disorders. Some neurodegenerative diseases are monogenic disorders with relatively well-characterized pathogenesis and pathophysiology (e.g., infantile spinal muscular atrophy due to mutations in the *survival motor neuron 1* gene).

When the natural history of such monogenic disorders is also well-characterized and relatively consistent (i.e., not highly variable), and when the expected treatment effect is large, self-evident, and closely associated temporally with the intervention, innovative clinical trial designs, rather than randomized, placebo-controlled trials, may be feasible to expedite clinical development.

In contrast, many other neurodegenerative disorders have a poorly understood etiology and/or pathophysiology, with a poorly characterized or highly variable natural history (e.g., sporadic amyotrophic lateral sclerosis or sporadic Alzheimer's disease).

For these disorders, randomized, placebo-controlled clinical trials, including crossover designs as appropriate, may be the most efficient means of obtaining persuasive evidence of effectiveness" (supra at p. 7)

How To Minimize Risks for Human Subjects

"For any neurodegenerative disorder, regardless of etiology, pathophysiology, and natural history, sponsors are encouraged to consider whether innovative trial designs (e.g., adaptive designs, enrichment designs, dose-controlled studies, or historical controls) both may be justified and may facilitate product development.

In all cases, however, to promote product development we encourage sponsors to discuss clinical development plans with FDA early in product development.

A. Study Design

• All subjects in trials of GT products for neurodegenerative diseases should receive the best standard of care, and no patient should be denied effective therapies in order to be randomized to a placebo-only arm.

While comparison to a placebo may be optimal to determine the effectiveness of some products, various strategies may be applied to minimize unnecessary exposure of subjects to placebo.

For studies involving placebo, FDA recommends add-on designs, in which a treatment previously shown to be effective for the neurodegenerative condition is given to all subjects participating in the trial, with subjects then randomized to receive the added GT product or added placebo.

Alternatively, as noted below, a randomized, concurrent-controlled, double-blind crossover trial may be considered if clinical circumstances are amenable to this type of study design" (supra at pp. 7-8). © {TBC}

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