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ISTAND Pilot Program Accepts First AI-Based Digital Health Technology

Go-To Guide:

- The U.S. Food and Drug Administration (FDA) accepted its first artificial intelligence (AI)-based and digital health technology-based project and the first in neuroscience into its ISTAND Pilot Program.
- The technology gathers a multitude of patient data to build a quantitatively informed profile of a patient's mental health, used to assist in monitoring and measuring treatment response, progress, and efficacy in clinical trials.
- FDA will now collaborate with the company to develop a Qualification Plan addressing the target population rationale and technical, clinical, and statistical considerations.
- As evidenced by the approved use, the FDA appears more comfortable with use of AI-based tools as supplementary tools rather than novel applications. Firms wanting to participate in the ISTAND Pilot Program should submit letters of intent according to the guidance described herein, noting that the ISTAND pathway to acceptance may be time-consuming.

The FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) accepted their first AI-based and digital health technology-based project and the first in neuroscience into its Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program.

ISTAND Pilot Program Expands Scope of DDT Qualification

The 21st Century Cures Act (the Act) formally established a multi-step process for the qualification of Drug Development Tools (DDTs) for a specific context of use (COU). Once qualified, the DDT may be used for the COU by any person in drug or biologics development. Following the passage of the Act, in 2020, the FDA launched the ISTAND Pilot Program designed to support the development of DDTs and expand the types of DDTs available to drug manufacturers beyond the scope of existing DDT qualification programs typically reserved for biomarkers and clinical outcome assessments. FDA envisioned various types of submissions to the program beyond novel biomarkers and clinical outcome assessments, including tools that may enable remote or decentralized trials, advance understanding of drugs, and leverage digital health technologies (*e.g.,* AI-based evaluation of patients or development of novel endpoints, wearables, etc.).

The qualification process includes three separate submissions: (1) Letter of Intent (LOI); (2) Qualification Plan (QP), and (3) Full Qualification Package (FQP).

Two years after its launch, in September 2022, the FDA's CDER and CBER accepted their first submission into the ISTAND program (Integral Molecular's Membrane Proteome Array), a tool to evaluate off-target protein binding of a variety of biotherapeutic modalities and potentially reduce or eliminate the need to conduct certain toxicology tests.

New DDT Combines AI with Emerging Technology and Challenging Therapeutic Area

The latest DDT accepted into the ISTAND Pilot Program comes from Deliberate.ai (Deliberate). Deliberate's AI-generated Clinical Outcome Assessment (AI-COA) leverages multimodal AI and behavioral signal processing technology to capture mental health symptoms and to evaluate the severity of cases of anxiety and depression. The tool gathers a multitude of patient data (*e.g.,* facial expressions, movements, pupil changes, speech, vital signs, etc.) to build a quantitatively informed profile of a patient's mental health. This data will, in turn, be used to assist in the monitoring and measurement of treatment response, progress, and efficacy in clinical trials.

Firms that would like to submit an LOI to the ISTAND Pilot Program may follow the Content Elements Guidance and submit LOIs to ISTAND@fda.hhs.gov. Following receipt and review of submission quality, drug development need, technological feasibility, and subject matter expert capacity, the applicant will be notified of their admission decision. When drafting information for submission, certain information will be made publicly available.

The FDA and Deliberate will now work together to develop a QP, a detailed proposal describing the information qualifying the DDT for the proposed COU in drug development, summarizing COU-supporting information, and identifying and proposing solutions to knowledge gaps. Deliberate's QP will also address the considerations detailed in the Appendix of the acceptance letter, including a rational for the target population (*i.e.*, adults 18-65 that demonstrate a broad severity range of a Major Depressive Episode (MDE) or are diagnosed with a Major Depressive Disorder (MDD) with certain exclusions for specified populations and certain psychiatric conditions) as well as technical, clinical, and statistical considerations.

Once Deliberate submits a satisfactory QP and proceeds to the FQP stage, it will be required to compile comprehensive supporting evidence informing the FDA's qualification decision for the DDT and COU. The FDA's final decision about whether a tool is qualified will be based on the FQP.

FDA Takes Prudent Approach to AI-Based Tools

AI-COA is not a biomarker or clinical outcome assessment, but rather improves the reliability of existing depression and anxiety severity measurement scales (ClinROs) "by adding another layer of information [from] multimodal combination of various signals." The FDA's current decision underscores the acceptance of the technology more for supplementary use than for novel drug development.

Like other regulatory schemes, the ISTAND program moves more slowly than the rate of technological advancement. Deliberate's path to acceptance took over two years: the company first submitted an application on Oct. 13, 2021, followed by a revised application on April 2, 2022, and it was deemed reviewable by the ISTAND program on July 29, 2022. As such, any firms wishing to participate in the program may face a lengthy timeline.

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