Regulatory Issues in the Return of Genetic Results
Potential FDA oversight and approval – SR IDE

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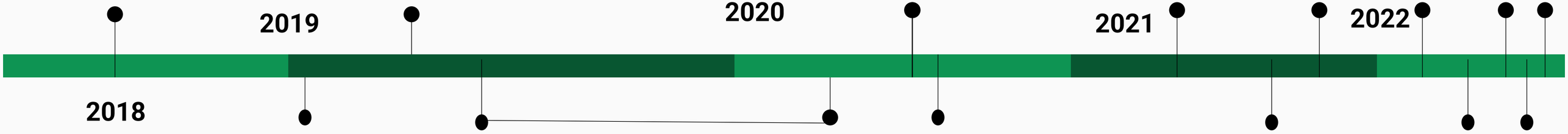
Beth Collins
Contractor, Research Compliance Branch
All of Us Research Program

National Institutes of Health

All of Us Research Program Return of Genetic Results (AoURP gRoR)



19 November 2018

FDA indicates the *All of Us* return of health-related genomic results is considered a Significant Risk Device Study

15 April 2019

All of Us requests Pre-Sub Meeting

24 January 2019

FDA recommends the use of a Pre-Sub process

28 May 2019 - 29 April 2020

FDA and *All of Us* Pre-Sub Conversations

06 June 2020

All of Us submits an IDE application

10 July 2020

FDA accepts the *All of Us* IDE application for the Return of Genetic Results (AoURP gROR)

01 April - 07 May

IDE Supplement

09 July 2021

IDE Progress Report at FDA

09 July 2022

IDE Progress Report at FDA

Adapted and Expanded from timeline in: Venner, E., Muzny, D., Smith, J.D. et al. Whole-genome sequencing as an investigational device for return of hereditary disease risk and pharmacogenomic results as part of the *All of Us* Research Program. Genome Med 14, 34 (2022). https://doi.org/10.1186/s13073-022-01031-z

All of Us Research Program Return of Genetic Results (AoURP gRoR)

FDA considers *All of Us* Research Program Return of Genetic Results (AoURP gRoR) investigational device to be the entire test system which includes sample collection, sample preparation, sequencing and genotyping, variant calling, variant interpretation, and generation of the test report provided to study participant.

PART 812 - INVESTIGATIONAL DEVICE EXEMPTIONS

§ 812.1 Scope.

(a) The purpose of this part is to encourage, to the extent consistent with the protection of public health and safety and with ethical standards, the discovery and development of useful devices intended for human use, and to that end to maintain optimum freedom for scientific investigators in their pursuit of this purpose. This part provides procedures for the conduct of clinical investigations of devices. An approved investigational device exemption (IDE) permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device. An IDE approved under § 812.30 or considered approved under § 812.2(b) exempts a device from the requirements of the following sections of the Federal Food, Drug, and Cosmetic Act (the act) and regulations issued thereunder: Misbranding under section 502 of the act, registration, listing, and premarket notification under section 510, performance standards under section 514, premarket approval under section 515, a banned device regulation under section 516, records and reports under section 519, restricted device requirements under section 520(e), good manufacturing practice requirements under section 520(f) except for the requirements found in § 820.30, if applicable (unless the sponsor states an intention to comply with these requirements under § 812.20(b)(3) or § 812.140(b)(4)(v)) and color additive requirements under section 721.

All of Us SR IDE Sponsor Responsibilities - 21 CFR 812

§ 812.40 General responsibilities of sponsors.
§ 812.42 FDA and IRB approval.
§ 812.43 Selecting investigators and monitors.
§ 812.45 Informing investigators.
§ 812.46 Monitoring investigations.

Per 21 CFR 812.40, as IDE sponsor, the *All of Us* Research Program is responsible for:

- selecting qualified investigators and providing them with the information needed to comply with the parameters of the IDE (i.e., genetic testing and return of results) properly,
- ensuring proper monitoring of the investigation,
- ensuring that IRB review and approval are obtained,
- submitting an IDE application to FDA, and
- ensuring that any reviewing IRB and FDA are promptly informed of significant new information about the investigation.

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The *All of Us* IRB is the single **IRB** of record for the AoURP gRoR IDE (G200165) and maintains compliance with the federal regulations outlined in 21 CFR 50 and 56.

The *All of Us* Research Program maintains approval from both the *All of Us* IRB and the FDA.

As the program intended to provide health-related genetic results in a non-clinical pathway, ***initial meetings with the FDA concluded that an IDE was required for the health-related return of genetic results to participants to ensure adequate risk mitigation.*** An IDE application was submitted to the FDA. On 09 July 2020, the FDA approved the AoURP gRoR IDE (G200165) application as a SR investigational device.

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As the IDE sponsor, the program selects investigators and monitors deemed qualified by training and experience to perform duties as assigned on the IDE approved pathway. IDE investigator responsibilities vary by the awardee's scope of work and are selected and vetted via a competitive, federal award process.

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A sponsor shall supply all investigators participating in the investigation with copies of the investigational plan and the report of prior investigations of the device.

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§ 812.46 Monitoring investigations.

(a) Securing Compliance
(b) Unanticipated Adverse Device Effects
(c) Resumption of Terminated Studies

§ 812.110 Specific Responsibilities of Investigators.

- Awaiting IRB/FDA Approval
- Informed Consent
- Protocol Compliance
- Supervising Device Use
- Financial Disclosure / COI

21 CFR 812 Subpart G - Records and Reports.

§812.140 Records.

(a) Investigator Records. A participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation…

(b) Sponsor Records. A sponsor shall maintain the following accurate, complete, and current records relating to an investigation…

(1) All correspondence… including required reports.
(2) Records of shipment and disposition.
(3) Signed investigator agreements including the financial disclosure information.
(4) …
(5) Records concerning adverse device effects (whether anticipated or unanticipated) and complaints.
(6) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

21 CFR 812 Subpart G - Records and Reports.

§812.150 Reports.

(a) Investigator Records. A participating investigator prepares and submits the following complete, accurate, and timely reports:

(1) Unanticipated adverse device effects.
(2) Withdrawal of IRB approval.
(3) Progress.
(4) Deviations from the investigational plan.
(5) Informed consent.
(6) Final.

(b) Sponsor Records. A sponsor shall maintain the following accurate, complete, and current reports relating to an investigation:

(1) Unanticipated Adverse Device Effects.
(2) Withdrawal of IRB Approval.
(3) Withdrawal of FDA Approval.
(4) Current Investigator List.
(5) Progress Reports.
(6) Recall and Device Disposition.
(7) Final Report.
(8) Informed Consent.

§ 812.145 Inspections.

§812.145(a) Entry and inspection. A sponsor or an investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).

§812.145(b) Records inspection. A sponsor, IRB, or investigator, or any other person acting on behalf of such a person with respect to an investigation, shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.

§812.145(c) Records identifying subjects. An investigator shall permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

Other Considerations from 21 CFR 812

Subpart A - General Provisions

§ 812.5 - Labeling of investigational devices.

§ 812.7 - Prohibition of promotion and other practices.

§ 812.10 - Waivers.

Subpart B - Application and Administrative Action

§ 812.20 - Application.

§ 812.25 - Investigational plan.

§ 812.35 - Supplemental applications.

§ 812.38 - Confidentiality of data and information.

Venner, E., Muzny, D., Smith, J.D. et al. Whole-genome sequencing as an investigational device for return of hereditary disease risk and pharmacogenomic results as part of the *All of Us* Research Program. Genome Med 14, 34 (2022). https://doi.org/10.1186/s13073-022-01031-z

§812.25 - IDE Investigational plan

Purpose - the name and intended use of the device and the objectives and duration of the investigation)

Protocol - a written protocol describing the methodology to be used and an analysis of the protocol demonstrating its scientific soundness)

Risk analysis - a description and analysis of all increased risks to the research subjects and how these risks will be minimized; a justification for the investigation; and a description of the patient population including the number, age, sex, and condition)

Description of this device - a description of each important component, ingredient, property, and principle of operation of the device and any anticipated changes in the device during the investigation)

Monitoring procedures - the sponsor's written procedures for monitoring the investigation and the name and address of each monitor.

Selected FDA References and Resources

FDA Regulations

- 21 CFR 812 - Investigational Device Exemptions
- 21 CFR 50 - Protection of Human Subjects
- 21 CFR 56 - Institutional Review Boards
- 21 CFR 54 - Financial Disclosure by Clinical Investigators
- 21 CFR 820 - Quality System Regulation

FDA Guidance

- Sponsor's Responsibilities For Significant Risk Device Investigations
- Investigators' Responsibilities For Significant Risk Device Investigations
- Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects
- Changes or Modifications During the Conduct of a Clinical Investigation
- Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring

Division of Industry and Consumer Education (DICE) - Email: DICE@fda.hhs.gov
Phone: 1(800) 638-2041 or (301) 796-7100, Press 2 to speak to the Industry Team

Thank You!

All of Us RESEARCH PROGRAM

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