Background
The All of Us Research Program is committed to the meaningful inclusion of participants of all backgrounds, health statuses, and walks of life from across the United States. However, there are sensitivities to conducting research that involves people, their data, or their specimens of which researchers must be aware. Furthermore, there are additional ethical considerations researchers must undertake when their studies involve participants, or information and samples that were donated by participants, who belong to certain groups that are most vulnerable to stigma and discrimination. Many of these groups have also been historically underrepresented in research, which means that past research results may be inaccurate or not apply to them the same way as groups that were represented. To ensure that the results of research studies capture the differences between groups of people in different circumstances, it is important that research studies utilize information from all kinds of people. Thus, it is crucial that All of Us, and users of resources produced and/or maintained by All of Us adhere to a set of ethical standards that support conscientious, culturally aware and competent research to minimize harm and engender trust.

Rule and Analysis
Human subjects research conducted, funded, or otherwise subject to regulation by the federal government must follow the Federal Policy for the Protection of Human Subjects, also known as The Common Rule (HHS: 45 CFR 46), a set of ethical standards that guide the conduct of research. The Common Rule defines a human subject as:

“… a living individual about whom an investigator (whether professional or student) conducting research:
(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
(ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.”

The Common Rule was based on, and codifies the provisions of, a document called the Belmont Report, published by the National Commission for the Protection of Human Subjects in 1976. The report outlined the general ethical principles that form the basis for biomedical and behavioral research with human research participants and provided guidelines to ensure such research is conducted according to those principles.

In the Belmont Report, three basic ethical principles were identified: respect for persons; beneficence; and justice.

Respect for Persons
The principle of respect for persons requires research participants be treated as autonomous agents. This means that research studies with human participants must respect participant’s autonomy, the ability of individuals to consider and make choices about their participation consistent with their own interests and goals.

The principle also requires that participants with diminished autonomy be protected. Certain individuals, because of any number of reasons, may not be capable of making informed choices for themselves about participating in research. These groups of people are considered vulnerable populations, or groups that are susceptible to coercion or undue influence by
researchers to do things that may not be in their best interests. The principle of Respect for Persons says that vulnerable populations are entitled to additional protections.

Under the Common Rule, several populations are afforded specific additional protections, above and beyond those afforded all human research participants; these populations include:

- Pregnant women, human fetuses, and newborns;
- Prisoners; and
- Children.

Some of these groups, like children and prisoners, are considered vulnerable populations. However, other populations—like individuals with decisional or cognitive impairments; economically, socially, or educationally disadvantaged individuals; and employees or students—can also be more susceptible to pressures to participate in research. Even though they may not be explicitly called out in the Common Rule, they are still entitled to additional protections.

**Beneficence**

The principle of beneficence requires that researchers working with human participants must try to ensure participants' wellbeing. To do this, the principle of beneficence posits several guidelines. First, research should not intentionally harm participants. While scientific discoveries are key to improving the human condition, the principle of beneficence maintains that these discoveries should not be made at great cost to participants.

In addition, beneficence stipulates that while participating in research always comes with some risks, these potential risks must be ethically justified by the potential benefit to society. In these cases, however, the principle of beneficence requires that:

- The possible benefits of the research must be maximized; and
- The potential harms of the research must be minimized.

Balancing these benefits and harms should include consideration of not only the benefits and harms to research participants, but also the benefits and harms to people generally as a result of the research. The decisions of how benefits to both the research participants and society at large are balanced against the risks of harm to the individual participant and society will depend on the context of each research project. Therefore, the decisions in one situation may not apply to all. The following example however illustrates a situation where obligations of researchers to beneficence may allow accepting some risks of harm to an individual research participant:

*Researchers studying ways to prevent STD infections may uncover the HIV status of a participant. Sharing that information back with the participant may help them get the right medical care but may also cause stress and anxiety. The obligation of “doing no harm” would justify returning that information to the participant. If we imagine now that the infected individual is a cis, heterosexual male with a pregnant cis female partner, the researchers will also have to consider whether sharing that information with his partner, for her wellbeing and for prevention of HIV transmission to the fetus, is appropriate. The obligation to maximize benefits and minimize harm, in this case extending it to the family of the research participant, may put the individual at risk of harm (emotional, social, etc.), if the researchers disclose that information to the participant’s wife, especially when the participant himself has not disclosed his HIV status.*
Justice
The principle of justice requires that benefits and harms resulting from research be distributed fairly amongst people. This means that participants should be included in research studies based on inclusion and exclusion criteria that are relevant to the research question and the potential research outcomes. Therefore, it is reasonable, in a study of food cravings during pregnancy, to exclude male participants and female participants who are not pregnant. But it is NOT reasonable to include only pregnant women from certain groups (e.g. socially or economically disadvantaged groups) because they are more easily influenced into participating in the study.

Furthermore, it is the responsibility of researchers to consider who will benefit from the outcomes of a research study when selecting which groups of participants to include or exclude in a study. As research studies are often associated with some amount of risk, it is important that researchers do not unfairly place the burden of those risks on groups of people who are unlikely to benefit from the research.

In addition to requiring ethical inclusion and exclusion criteria, the principle of justice demands that researchers consider the downstream effects of research, like the discovery of a new medical treatment or procedure. Particularly if the study receives funding from the government, the principle of justice calls for researchers to ensure that people benefit from the research according to need, not according to who can afford the treatment.

Conclusions
Most kinds of research using the All of Us scientific resources will not be considered human subjects research under the Common Rule because this research:
- Will not include either direct participant contact or identifiable data or biospecimens; and
- The data has been carefully curated to help prevent it from identifying All of Us participants, while preserving its scientific utility.

However, it’s important for individuals using All of Us scientific resources to acknowledge the conditions under which participants have consented to the use of their information and to respect those conditions. Furthermore, it is helpful for All of Us data users to remember that research cannot and should not necessarily treat all groups of participants in the same way, that some groups are more susceptible to certain risks associated with research than others, and that fair treatment, rather than equal treatment, should be the goal.

Moreover, while most researchers using the All of Us scientific resources won’t be conducting human subjects research, it doesn’t mean their studies can’t do harm. Harms do not consist only of physical harm; there are many kinds of harms, including psychological, social, and economic harms. It’s important that researchers understand the impact their research results could have on individuals, communities, and society so that they can take steps to keep negative impacts to a minimum.

Finally, research using the All of Us scientific resources can result in both harms and benefits. Users of the All of Us scientific resources must be careful that those benefits and harms are fairly and equitably distributed. Furthermore, individuals using the All of Us scientific resources for research should carefully consider the research questions they are attempting to answer. Their study sample should include all populations that are relevant to answering their research question and should exclude populations and individuals who might disproportionately suffer as a consequence.
Policy Statement

Though not required by law, researchers using the All of Us scientific resources are expected to follow the ethical principles guiding research with human research participants, including the principles of Respect for Persons, Beneficence, and Justice. Doing this will help ensure that the research studies conducted using All of Us scientific resources make the greatest possible positive change, while doing the least possible harm, to human wellbeing. Conducting ethically sound research thus affirms commitment to the core values of the All of Us Research Program by respecting the dignity and choices of participants as partners and actively considering the vulnerabilities and disadvantages of diverse individuals and communities.