Protocol Cover Page

Study title: Characterizing Late-season Influenza Vaccine Responses to Compare the 2023 and 2024 Vaccine Formulations

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Institutional Review Board
Human Subjects Protocol Narrative

Human subjects protocol narrative – Version 2.1 August 17th 2021

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1. Project Title
Characterizing late-season influenza vaccine responses to compare the 2023 and 2024 vaccine formulations
2. Principal Investigator
Tal Einav, PhD
3. Summary
Provide a brief overview on the proposed study in lay language (no more than one paragraph).
Every 1-2 years, the seasonal influenza vaccine composition changes to include updated viruses, yet the precise effects of updating the vaccine remain understudied. Since the vaccine formulation for each season (with a season defined as starting in July and ending the following June) expires on June 30, vaccine formulations cannot be compared head-to-head. Thus, the 2023 and 2024 vaccines have only been compared by analyzing people given the former vaccine in the fall of 2023 and people given the latter vaccine in the fall of 2024, and baseline repertoires may have greatly changed over the course of that year. To that end, we intend to vaccinate a small cohort with the 2023 influenza vaccine between May-June 2024, which will let us compare between individuals receiving the 2023 vaccine last fall, the 2023 vaccine late in the season (our cohort), and the 2024 vaccine next fall. **June 2024 Amendment:** We will investigate whether the late-season 2023 vaccine primed this cohort to respond better to the standard 2024 vaccine with standard timing (vaccine administered around September-October).

4. Project Personnel	
Please utilize the Human Subjects Protocol Personnel Attachment to list all personnel engaged in human subjects research on this project. Personnel (including offsite collaborators) should be listed if they will: • be involved with planning and designing the study • intervene with subjects by performing research procedures • participate in the recruitment and/or selection of subjects • participate in the informed consent process • have access to subject identifiable data	
Check to confirm that current Protocol Personnel Attachment is included with this submission	☒ Yes
Please ensure that training certificates are on file with the IRB for all individuals listed. CITI "Protecting Human Research Participants" online course Please note: In the case of NIH-funded human subjects research, all individuals who are involved with the design or conduct of the research must complete Human Subjects Training	

5. Biospecimens/Data				
Biospecimens and/or data will be collected specifically for this research project	Yes	☒	No	☐
Existing biospecimens and/or data will be used for this project	Yes	☐	No	☒

List the materials from human subjects (this may include specimens, records, or data) that will be utilized for this project.

Type of Samples	**Source of Samples**
Example: Blood samples	*Collected by clinical collaborators at University of Virginia*
Blood samples	Collected by the LJI Clinical Core

6. Specific Aims

Briefly describe the purpose, specific aims, or objectives of the study. State the hypotheses to be tested. Emphasize those aspects that justify the use of human subjects.

Aim 1: Do the 2023 and 2024 influenza vaccine formulations elicit markedly different antibody responses? Influenza vaccines are primarily assessed by measuring how potently an individual's serum inhibits hemagglutination of different influenza variants. We will administer the Fluzone, an approved seasonal influenza vaccine with demonstrated efficacy in adults, and collect serum from each vaccinee at day 0 (right before vaccination), day 28 (the peak vaccine response), and day 90 (to test how rapidly their antibody response wanes). Previous vaccine studies have shown that updating the seasonal vaccine leads to different antibody responses. Our cohort will identify whether such differences arise from different exposure histories or from the different vaccine formulations.

Aim 2: Does administering the 2023 vaccine in the fall versus later in the season affect the subsequent antibody response? By comparing antibody responses in our cohort versus responses from influenza vaccine studies carried out in September-November 2023, we will quantify whether administering the vaccine 6-8 months later leads to fundamentally different responses. If vaccine responses look identical, it will obviate the need for late-season vaccine studies, whereas if they look markedly different it will emphasize a need to decouple exposure background from vaccine responses when comparing results across years.

Aim 3: Determine which factors affect the antibody response post-vaccination. Using vaccine studies from the past decade, we have quantified how various factors (*e.g.*, age, sex, BMI) affect the antibody response. In this study, we are adding two additional factors within our questionnaire – how much do you exercise and how much sleep did you get the night before – that have been demonstrated to affect the vaccine response to influenza and other pathogens [Rayatdoost 2022, *Yale J Biol Med*]. Comparing this cohort to other publicly available vaccine studies, we will quantify the impact of both features in the vaccine response.

June 2024 Amendment

Aim 4: Does administering the 2023 vaccine late in the season prime the subsequent 2024 response? By comparing antibody responses in our cohort versus responses from other influenza vaccine studies (where participants are annually vaccinated), we will quantify whether this prime-boost regime leads to fundamentally stronger or longer-lasting responses.

7. Background and Significance

Provide relevant background information to justify performing the proposed study. Describe any relevant preliminary data. Indicate the significance of the research based on the existing literature and how will it add to existing knowledge.

The unparalleled impact of the ongoing COVID-19 pandemic and the four pandemics caused by influenza viruses over the past century underscore the significant threat respiratory viruses pose to human health. By the end of 2023, COVID-19 had resulted in over 100 million infections in the United States alone (WHO). Similarly, influenza caused ~26 million infections in 2022-23 and ~45 million infections in 2023-24 thus far (CDC). One of the major challenges we face, if we wish to successfully combat a future pandemic, is the establishment of strong and durable immune memory against these viral threats. Currently, both SARS2 and influenza viruses evade vaccine induced responses and must be regularly reformulated to generate protective immunity, yet the repercussions of the many choices that must be made during vaccine selection, especially the choice of the vaccine's composition, remain poorly understood. Quantifying the differences between individuals receiving the 2023 and 2024 vaccines as close together in time as possible will clarify the effect of changing the vaccine.

The Einav lab has developed a unique framework to use baseline (day 0) antibody inhibition profiles to predict the subsequent response at day 28 and day 90 post-vaccination. Our models are trained using prior vaccine studies to predict the outcomes of future responses. We have demonstrated our predictive power on influenza vaccine data from every season from 2014-15 to 2023-24 and used these methods to quantify the different effects from each year's vaccine. For example, we found that the 2023 vaccine elicited ~2x lower fold-change in H3N2 serum hemagglutination

compared to the 2022 vaccine (even though both contained the same H3N2 vaccine strain), demonstrating that the immune background can substantially affect the vaccine response.

Using this cohort, we will quantify the vaccine responses between: (1) previous vaccine studies administered last fall using the 2023 vaccine, (2) our late-season study administering the 2023 vaccine, and (3) future vaccine studies next fall administering the 2024 vaccine. In each case, we will analyze the peak vaccine response (at day 28) and its durability (by assessing vaccine waning at day 90) as well as quantify how accurately each vaccine cohort can predict the other cohorts to disentangle the effects of exposure background and vaccine composition. In doing so, we will demonstrate a means to rigorously assess vaccine responses across seasons without the confounding effects of different immune backgrounds.

June 2024 Amendment: Using the cohort from this study, we will quantify the vaccine responses of people receiving the influenza 2024 vaccine whose previous vaccine was either administered: (1) in May/June [our late-season vaccine study] or (2) in the Fall of 2023 [using other annual vaccine studies]. In each case, we will analyze the peak vaccine response (at day 28) and its durability (by assessing vaccine waning at day 90) as well as quantify how accurately each vaccine cohort can predict the other cohorts. Our goal will be to demonstrate whether such late-season vaccine administration can boost subsequent vaccine responses.

8. Estimated Duration of the Project

State the duration of the entire study from opening of study for participant recruitment through end of follow up and data analysis to project completion.

We estimate the study will take 10 years starting in 2024 and ending in 2034.

9. Subject Population

Describe the characteristics of the proposed subject population.
Include:

1. Total number of participants to be studied
2. Age
3. Gender
4. Ethnic background
5. Health status

State the inclusion and exclusion criteria for participants to be enrolled on this study.

Indicate whether any vulnerable groups such as children, pregnant women, prisoners, adults unable to consent will be included and provide rationale for involving such participants.

We anticipate enrolling 25-60 donors. Study participation will not be limited to donors of any specific race or ethnic background.

June 2024 Amendment: Only donors who received the late-season 23-24 vaccine will be eligible to continue and receive the 2024-25 vaccine in Sep-Nov, since we only want participants who had been given a late-season influenza vaccine.

Inclusion Criteria
All of the donors will correspond to the following criteria:

- Be between 18-64 years of age
- Males or non-pregnant, non-nursing females
- Weigh at least 85 pounds for whole blood draw
- Ability to provide signed informed consent
- Subjects must plan to receive the intramuscular influenza vaccine at LJI

Vaccinated at LJI:
All subjects will receive the approved intramuscular quadrivalent Fluzone influenza vaccine for the 2023 season at LJI. Enrollment will begin in May, and subjects will receive their vaccine before its expiration date at the end of June 2024. Every year the LJI clinical core offers a seasonal influenza vaccination program for LJI employees, the Clinical Core licensed nursing staff are trained in administering these vaccines. All vaccinations are administered under current standing orders on file by the LJI Medical Director, Dr. Marcia Isakari.

June 2024 Amendment: All subjects will now receive the approved intramuscular quadrivalent Fluzone influenza vaccine for the **2024 season** at LJI. These vaccines will be administered before December 2024.

Exclusion Criteria:
All of the donors will correspond to the following criteria:

- Received an influenza vaccine in the past year
- HIV, HBV, HCV infection
- History of certain anemias
- Presence of significant cardiovascular disease, systemic diseases including, but not limited to, diabetes which is not controlled, renal disease, liver disease, malignancy, infection, or blood clotting disorder
- Inability to provide informed consent
- Recent whole blood donation within 56 days or leukapheresis within 112 days
- Children (under 18 years of age), elderly (65 years of age or older), pregnant or nursing females
- Individuals with egg allergies
- Has ever had Guillan-Barré syndrome

We will not include vulnerable groups such as pregnant women, prisoners, or adults unable to consent.

10. Subject Identification and Subject Recruitment

Describe the methods that will be used to identify potential subjects. Such as existing database search, collaboration with specific physicians or organizations, public advertisements.

Describe how subjects will be recruited; when, where and by whom.

Copies of all materials that will be used to recruit subjects must be included with this submission. This includes: advertisements, flyers, letters, text of social media posts, ResearchMatch advertisements etc.

Advertising may take place through IRB approved flyers posted at LJI, the LJI website, institute emails, the extensive clinical core donor database, and flyers posted on social media. During enrollment, the study design will be explained, so that participants know that two follow-up visits at day 28 and day 90 are expected of them. Eligible subject will be asked if they are willing to receive the intramuscular Fluzone vaccine, with the number of participants capped at 60 or depending on vaccine availability. Participants will be tracked on the donor tracking sheet.

Potential volunteers may also be solicited by word of mouth, which means telling coworkers at LJI about the study, or LJI employees talking to their colleagues, friends, and family about the possibility of participating or to anyone expressing interest in participating in LJI clinical research. LJI Clinical Core phone and email may be given out to prospective subjects and it's up to the prospective subject to contact LJI Clinical Core to participate. All Potential donors may contact the clinical core via LJIs website Participants will be asked to fill out a pre-screening questionnaire to collect relevant vaccine history information to determine study eligibility. Such as;

- Did you receive the influenza vaccine last year (2023-2024)? (Yes/ No)
  - If yes- this participant will be excluded from our study
- Did you receive the influenza vaccine two years ago (2022-2023)? (Yes / No)
  - If yes- Which vaccine did you receive? (intramuscular/intranasal)
- Did you receive the influenza vaccine three years ago? (Yes/ No)
  - If yes- Which vaccine did you receive? (intramuscular/intranasal)
- Have you been diagnosed with influenza in the past year? (Yes/No)

- If yes- When were you diagnosed with influenza?
- Have you ever had an adverse reaction to a dose of influenza vaccine? (Yes/ No)
- Do you have an allergy to eggs? (Yes/ No)
- Have you received another vaccine (not an influenza vaccine) in the past 14-days? (Yes/ No)
  - If yes- What vaccine did you receive?
  - If yes- When did you receive the vaccine
- Do you have any illnesses that would give you concern during a blood donation?

An IRB approved flyer may be shared with friends, colleagues, on LJI's website or to anyone expressing interest in participating in LJI's clinical research.

Participants will be welcome to withdraw from the study at any point. Moreover, we will analyze the samples as they are received, and if the day 0 or day 28 samples show no measurable serum inhibition we will not proceed with the subsequent time points. In addition, if the number of subjects we enroll is <25 either at the beginning of the study or because of drop-out, we may opt to not proceed with subsequent time points. Fewer than 25 participants would not yield enough data points for meaningful results.

11. Study Design and Methods

Describe the research design and the procedures to be used. Clearly describe what a subject in this study can expect to happen to them. Include a clear description of the procedures/activities associated with the study including where the procedures/ activities will be done, what will be done at each study visit, as well as the participant's time commitment for each study visit and the total duration of the participant's involvement in the research. If questionnaires/surveys will be completed as part of the research, a copy should be included with the protocol submission.

Describe the type of analysis to be performed on biospecimens/collected data. Indicate whether any genetic analysis is to to be performed or any cell lines are to be created.

Indicate whether any test or experiment results will be returned to subjects.

A potential subject will be verbally consented by LJI Coordinators to take part in an initial telephone or in person screening questionnaire (see attached). If the donor meets all eligibility criteria, they will be consented to enroll into the study. The enrollment consent will be obtained via the phone or over email. All subjects will be given as much time as needed to review the consent form and ask any questions they may have regarding the study. This is described in more detail below in Section 19 (Informed Consent). As described in the Informed Consent, participants can withdraw from the study at any point.

The study is designed such that we will capture participants pre-vaccination, at their peak-immune response (day 28), and at a longer-term time point to assess durability (day 90). Once informed consent is obtained, we will obtain a blood draw (20 mL) at each time point. After their first blood draw at day 0, each participant will be given the 2023 influenza Fluzone vaccine.

The anticipated time points are:

- May/Jun 2024, Day 0 after the first vaccination: **Vaccination** and 20 mL blood draw
- Jul 2024, Day 28 after the first vaccination: 20 mL blood draw
- Sep 2024, Day 90 after the first vaccination: 20 mL blood draw
- Sep-Nov 2024, Day 0 after the second vaccination: **Vaccination** and 20 mL blood draw
- Dec 2024, Day 28 after the second vaccination: 20 mL blood draw

Feb 2025, Day 90 after the second vaccination: 20 mL blood draw
Influenza vaccines typically become available in September or October, and we will administer them as soon as they are purchased. The range (Sep-Nov) of the second vaccination date will ensure that the second round of vaccines will be available and help accommodate any schedule conflicts for participants.

We will try to adhere to this schedule, but we expect that not all participants will return at exactly day 28 or day 90 after either vaccination, and we will mark down their exact dates for their post-vaccination visits. Deviations by as much as 2 weeks are acceptable, since the antibody response is known to peak around day 7-14 and then stays at this maximal level for at least 1 month.

Prior to study visit at LJI, all potential donors will have a phone/email screening to ensure that they are safe to donate. They will also be asked on the day of donation if there have been any changes since the phone/email screening.

We are asking for a small blood draw at each visit. The blood sample will be withdrawn from their arm with a needle through standard blood collection by a certified phlebotomist or nurse. For the whole blood draw, two SST tubes (~10 mL per tube) will be obtained. After the sample is collected, light pressure will be applied by a pressure bandage to help control and stop the bleeding. We will follow national blood bank guidelines.

Participants may decline or opt to stop the sample collection or examination at any point in time. The medical provider performing the examination may also stop the examination or sample collection at any time if they determine it is not in the participant's best interest (e.g. medical risk, unacceptable distress or discomfort).

The Intramuscular Influenza Vaccine Fluzone (Quadrivalent Inactivated Vaccine)
The intramuscular muscular influenza vaccine Fluzone is an approved seasonal vaccine that contains 4 (quadrivalent) types of influenza: influenza A (H1N1), influenza A (H3N2), and 2 influenza B viruses. An LJI clinical staff nurse will begin by explaining the procedure. Next, nursing staff will aseptically clean the upper arm (deltoid muscle) and inject the vaccine. Participants may be monitored for up to 15 minutes following the vaccination.

Specimens and Data
a) Specimen handling:
All specimens will be handled using universal precautions. Samples will be collected into coded containers, labeled with the subject's coded study ID number and date with no other personal, identifying information. After samples are drawn, the coded sample will be transferred (by study coordinator or designated study personnel) to the LJI processing facility where the sample will be processed (spun down in a centrifuge) and then stored. Personal identifying information will not be shared with anyone outside of the LJI Clinical Core staff.

b) Data:
At the time that subjects are screened for the study, they will be asked if they are willing to provide clinical information regarding vaccination history, which will be recorded on a coded questionnaire with the study subject ID and either stored on paper or entered into a password protected online database at LJI. This will allow research investigators to access coded clinical information to correlate with the results of the research studies being performed at LJI. The coded donor information uploaded into the database may include a) demographics like race and ethnicity, age, gender, postal code, and pertinent medical history including comorbid conditions, influenza diagnosis, influenza vaccination history, COVID-19 testing, exposure and other social history, treatments received for COVID-19, symptoms and date of onset/resolution, clinical laboratory testing (e.g. complete blood count, renal and liver function testing), vaccination history and b) blood draw information (volume and date drawn). All research samples, whether at LJI or elsewhere, will only be known to researchers by the Donor ID, and never will personal identifying information about the donors be shared with laboratory personnel or anyone who is not affiliated with the LJI Clinical Core.

No sensitive information will be requested nor is needed for this study (such as Drug & Alcohol abuse treatment records, Mental Health/Psychiatric treatment records, HIV test results, or genetic test results).

Analysis
Serum samples will be used to assess the antibody response using hemagglutination inhibition, a serological assay that quantifies how strongly the antibody response can prevent an influenza variant from binding to red blood cells. This is a standard assay used to determine vaccine effectiveness, with hemagglutination levels ≥40 corresponding to ≥50% protection against influenza. No results from these tests will be returned to participants. The fact that results will not be returned to participants is detailed in the consent form and will be verbally said to the subjects by LJI Clinical Coordinators.

12. Potential risks

Describe all potential or known risks and discomforts associated with participation in the study Assess their likelihood and seriousness. If data is available, estimate the probability that a given risk may occur, its severity and its potential reversibility. Include the risks associated with loss of confidentiality.

Risks of Intramuscular Influenza Vaccination: Receiving an intramuscular influenza vaccine may result in soreness, redness, swelling where the shot was given, fever, muscle aches, and headache are also possible after receiving the vaccine. There is a very small elevated risk of Guillain-Barré Syndrome (GBS), after the inactivated influenza vaccine. This entails a rapid progressive paralysis; however, most people recover fully. These side effects are all CDC recognized risks following inactivated influenza vaccination.

Risks of Blood Draws: Taking blood may cause some discomfort, bleeding, or swelling/bruising where the needle enters the body, and in rare cases, fainting, dizziness or infection.

Risk of Loss of Confidentiality: Although we will make every effort to protect the subject's privacy and confidentiality it is possible that the subject's participation in this study could become known to others. The study team has put protections in place to protect the confidentiality of subjects, which are described in the risk management and confidentiality sections below.

13. Risk Management Procedures

Describe procedures for minimizing any potential risks, including risks to confidentiality, and assess their likely effectiveness. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Also, where appropriate, describe the provisions for monitoring the data collected to ensure the safety of subjects.

Risk Management of Blood Draws: Standard care will be used during blood draws. Volunteers who do not meet the appropriate inclusion/exclusion criteria will not be included in the study.

Risk Management of Vaccine Administration: These procedures will only be carried out by trained medical professionals in an appropriate clinical setting following explanation of the procedure and agreement by the participant to proceed.

Risk Management of Loss of Confidentiality: In order to maintain participant confidentiality, all laboratory specimens and other records will be identified by a coded number only. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant except as necessary for monitoring by the FDA or LJI Institutional Review Board (IRB). In the event of reported or suspected abuse or neglect, research staff will report such information to the appropriate authorities. Research staff training includes procedures for reporting.

14. Potential Benefits

Describe those benefits to be gained by the individual subject, scientific community, and/or society by conducting this study. If there is no anticipated direct benefit to the subject, this must be stated.

Participants will receive their 2023-24 seasonal influenza vaccine at no charge, and past vaccine studies have demonstrated that post-vaccination antibody levels remain elevated for at least 1 year in healthy adults, which should offer cross-reactive protection in the 2024-25 season. The investigators may learn more about the strength and durability of the antibody response following intramuscular vaccine administration.

June 2024 Amendment: Participants will receive their 2024-25 seasonal influenza vaccine at no charge, which should provide the best possibility of protection for that influenza season.

15. Risk/Benefit Ratio

Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result.

It is the opinion of the investigators that the benefits outweigh the risks. The potential to future patients and society as a whole outweigh the small risks associated with the study. Procedures have been put in place to minimize the risk to individual subjects. The risk/benefit ratio is favorable.

16. Alternatives to Study participation
Indicate if there are any alternatives to participation in this study that are available to the participant. If the study does not involve any kind of treatment or direct benefit to the participant please state that the alternative is simply not to participate.
Participants may choose not to participate in this study at any time.
17. Compensation to participant
If subjects are to be paid for participation in the study, the amount and schedule of payment(s) must be indicated here and in the informed consent document. If subjects are to be reimbursed for transportation expenses, meals, time away from work, etc., this should also be stated. Indicate how and when payments will be made.
For each blood draw, participants will receive $25 in compensation. If a subject has traveled to LJI and is ineligible to participate in the study through no fault of their own (e.g., unsuitable veins to draw blood), the subject may be reimbursed $25 for time, at the discretion of the study coordinator. Payment will be made by LJI study coordinator(s) after completion of each study visit using standard repayment procedures. Payments may be issued in the form of a check immediately after the donation, or it may be mailed to subject's provided mailing address. As a benefit for participating, LJI merchandise of no more than $20 value may be offered to participant (e.g., LJI water bottle). All donors will be asked to complete a W-9 form for accountings records. The W-9 may be shared with the LJI accounting department in order to issue the donor a 1099-MISC form if the donor exceeds $599 in payments in a single calendar year.
18. Costs to participant
If the study involves the possibility of added expense to the subject, describe that here and indicate who will be responsible for these costs.
There is no cost to subjects for participation.
19. Informed consent
Please describe how and by whom informed consent will be obtained, describe the consent procedures to be followed, including the circumstances under which consent will be sought and obtained, and the method of documenting consent. Attach informed consent documents to be used. If a waiver or alteration of informed consent is being requested please refer to the criteria for granting such a waiver and provide justification for waiving or altering consent requirements Indicate if oral consent only will be obtained for any part of the study, for example administration of pre-screening questionnaire. In this case confirm that this presents no more than minimal risk to the subject and relates only to procedures that do not normally require written informed consent outside of the research context.
After contacting the study coordinator(s) and if all eligibility requirements are met, subjects will be given a copy of the approved informed consent form either in person, through mail or email. LJI study coordinator(s) will verbally explain the study (in person or via telephone if consent form was mailed or emailed), allow the donors time to read the consent form, discuss any questions or concerns after review of the consent form, and give additional explanations by contacting the P.I. if necessary. In all cases, LJI study coordinator(s) will obtain written consent prior to study enrollment and study procedures. This can be given to the study coordinator(s) in person or via email, mail, or fax. By signing the consent forms, donors are consenting that they have had the opportunity to ask questions and that all their questions have been answered. The consenting study coordinator will also sign the consent form to ensure all questions have been answered. Signed consent forms will be stored by the clinical coordination team in a locked filing cabinet. See consent for specific language. **June 2024 Amendment:** During their fourth visit (Sep-Nov, before receiving their second vaccine), all participants will be reconsented with this amended informed consent document.
20. Privacy

Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact with or whom they provide personal information.

Subject interaction will be limited to the study personnel at LJI and the certified phlebotomists at LJI. These persons will not disclose any identifying information to research staff or anyone else and will maintain the privacy of all study participants that are screened and/or consented.

21. Confidentiality

Describe what provisions will be used to maintain confidentiality of participant and study data/specimens. For example, How will participant and study data/specimens be protected/secured? Will the research records be in a locked cabinet? Who will have access to the records? What security procedures will be used regarding electronic storage of data? Who will control access to the records and how will this be controlled? What are the procedures for "coding" participant/study information/specimens? Where will data key be kept? Indicate what information/samples, if any, will be disclosed to entities beyond the PI and key personnel noted in the application, and to whom the information will be provided.

All LJI research staff have undergone the CITI Biomedical Human Research training.

Data Security: Any data collected as part of this study that is stored and/or is transferred via the internet will follow our data security process as outlined below.

With fast-developing technology, dependable and comprehensive data security measures are key components to defy the perceived threats of internet hackers and accidental disclosure of confidential information. In the following, we provide a summary of the key features pertinent to this project:

- An anonymous participant identification number is used for all data collection, recording, and submission to the project database.
- Data that contain any participant identifiers (e.g., name or contact information) other than the unique identifier are password protected and accessible only to staff members whose job requires knowledge of such data.
- Laboratories are instructed not to disseminate any participant identifiers in any communications with, or data submissions to, any other collaborators. Any data transfer over the Internet uses encryption.
- Data transfer and all Web-based utilities use secure access (user and server authentication, 128-bit SSL encryption). This type of encryption is the same as is used for Web-based transactions that involve credit cards or Web banking.

All stored samples are accessible only to the appropriate study members. In addition to the above listed confidentiality and security procedures, our approach will comply with all requirements of relevant federal, state, and LJI regulations.

22. Disclosure of Financial Interest / Conflict of Interest

Indicate whether the PI or any other personnel associated with this study have any financial interests related to the research.

"Financial Interest Related to the Research" means any of the following interests in the sponsor, product or service being tested, or competitor of the sponsor or any for-profit company collaborating on the research held by the individual or the individual's immediate family:

- Ownership interest of any value including, but not limited to stocks and options exclusive of interests in publicly-traded, diversified mutual funds.
- Compensation of any amount including, but not limited to honoraria, consultant fees, royalties, or other income.
- Proprietary interest of any value including, but not limited to, patents, trademarks, copyrights, and licensing agreements.
- Board or executive relationship, regardless of compensation.

Describe the relationship in enough detail to determine whether it could be considered a conflict of interest. A financial conflict of interest can be defined as a financial association that would cause an investigator to prefer one outcome to another.

Indicate whether the PI or any other research personnel associated with the study have any other (non-financial) conflict of interest related to the research that could affect the rights and welfare of the human subjects.
All financial interests related to the research should be disclosed to subjects on the informed consent document.

None.

23. Certification of Principal investigator's Responsibilities

By signing below I agree/certify that:

1. I have reviewed this protocol submission in its entirety and that I am fully cognizant of, and in agreement with, all submitted statements.
2. I have adequate resources and facilities to carry out the proposed research.
3. I will conduct this research study in strict accordance with all submitted statements except where a change may be necessary to eliminate an apparent immediate hazard to a given research subject.
4. I will notify the IRB promptly of any change in the research procedures necessitated in the interest of the safety of a given research subject.
5. I will request and obtain IRB approval of any proposed modification to the research protocol or informed consent document(s) prior to implementing such modifications.
6. I will ensure that all co-investigators, and other personnel assisting in the conduct of this research study have access to the entire current version of the research protocol and are fully informed of the current (a) study procedures (including procedure modifications); (b) informed consent requirements and process; (c) potential risks associated with the study participation and the steps to be taken to prevent or minimize these potential risks; (d) adverse event reporting requirements; (e) data and record-keeping requirements; and (f) the current IRB approval status of the research study.
7. I will not enroll any individual into this research study: (a) until such time that the conduct of the study has been approved in writing by the IRB; (b) during any period wherein IRB renewal approval of this research study has lapsed; (c) during any period wherein IRB approval of the research study or research study enrollment has been suspended, or wherein the sponsor has suspended research study enrollment; or (d) following termination of IRB approval of the research study or following sponsor/principal investigator termination of research study enrollment.
8. I will not enroll any individual into this research study until such time that I obtain his/her written informed consent, or, if applicable, the written informed consent of his/her authorized representative (i.e., unless the IRB has granted a waiver of the requirement to obtain written informed consent).
9. I will employ and oversee an informed consent process that ensures that potential research subjects understand fully the purpose of the research study, the nature of the research procedures they are being asked to undergo, the potential risks of these research procedures, and their rights as a research study volunteer.
10. I will ensure that research subjects are kept fully informed of any new information that may affect their willingness to continue to participate in the research study.
11. I will maintain adequate, current, and accurate records of research data, outcomes, and adverse events to permit an ongoing assessment of the risks/benefit ratio of research study participation.
12. I am cognizant of, and will comply with, current federal regulations and IRB requirements governing human subject research including adverse event reporting requirements.
13. I will make a reasonable effort to ensure that subjects who have suffered an adverse event associated with research participation receive adequate care to correct or alleviate the consequences of the adverse event to the extent possible.
14. I will ensure that all listed investigators have the appropriate credentials to conduct the portion of the study in which they are involved.

PI Signature: Tal Einav **Date:** 2024-07-22