Protocol Title: **A Pilot Study of the Immunogenicity of a Two-dose Protocol for 9-valent Human Papilloma Virus Vaccination in Postpartum Girls and Women (15-45 years old) previously unvaccinated against HPV**

NCT No.: **04274153**

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JHM IRB - eForm A – Protocol

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1. Abstract

The human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the United States (U.S.) and is responsible for a wide range of conditions, including cancers within the anogenital tract and the oropharynx. Each year in the U.S., HPV causes approximately 330,000 cases of precancerous cervical dysplasia and 12,000 cases of cervical cancer, the most common cancer in women attributable to HPV. In 2012, there were 249,512 prevalent cervical cancer cases and 4,092 deaths in the U.S. Although infection with HPV is extremely common and most women will become infected with HPV at some point in their lives, the majority of infections are asymptomatic. However, if infection persists, over time, precancerous disease can eventually develop into cancer and spread through the body. In October 2018, the FDA expanded the approved use of the HPV 9-valent vaccine to include mid-adult women and men 27-45 years of age. This vaccine prevents cervical cancer caused by 9 types of HPV, however the immunization rate in the US is poor. As most pregnant women receive some prenatal care, the postpartum period is ideal to educate and implement a HPV vaccination program. The vaccine requires three doses and some patients have a difficult time completing the series. Our objective of this pilot study is to determine whether a two-dose 9-valent HPV vaccination regimen is non-inferior to a three-dose regimen.

Research Hypothesis

A 2-dose HPV vaccination regimen will demonstrate a non-inferior immune response compared to historical controls who received a 3-dose regimen among 15-45 year old postpartum women.

Research Justification

One of the main reasons the HPV vaccine has had such poor compliance is lack of access to care. Vulnerable women that would benefit most from the HPV vaccine are often otherwise healthy individuals with minimal interactions with the healthcare system. However, as most pregnant women receive some prenatal care, the postpartum period is ideal to educate and implement a HPV vaccination program. Prior studies demonstrate <15% of pregnant women had received any doses of HPV vaccine and <8% completed the series. Given this window of opportunity, a few investigators have implemented postpartum HPV vaccination at their institutions, and the Departments of Health in the states of New York and Washington recommend it for women who have not completed the series.

2. Objectives (include all primary and secondary objectives)

Our primary aim is to determine whether a two-dose 9-valent HPV vaccination regimen is non-inferior to a three-dose regimen. The first dose will be given after giving birth while inpatient.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

The human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the United States (U.S.) and is responsible for a wide range of conditions, including cancers within the anogenital tract and the oropharynx. Each year in the U.S., HPV causes approximately 330,000 cases of precancerous cervical dysplasia and 12,000 cases of cervical cancer, the most common cancer in women attributable to HPV.[1] In 2012, there were 249,512 prevalent cervical cancer cases and 4,092 deaths in the U.S. Although infection with HPV is extremely common and most women will become infected with HPV at some point in their lives,[2] the majority of infections are asymptomatic.[3,4] However, if infection persists, over time, precancerous disease can eventually develop into cancer and spread through the body.

Prophylactic HPV Vaccine

In 2006, the Federal Drug Administration (FDA) approved a quadrivalent HPV vaccine that prevents infection against four common HPV types (i.e. 6, 11, 16, and 18) that are responsible for 70% of cervical cancer cases. The vaccine is administered as a series of three doses at 0-months, 1-2 months, and 6-months. Then in 2014, the FDA approved a 9-valent vaccine that prevented infection from five additional HPV types (31, 33, 45, 52, and 58) that are responsible for 20% of cervical cancers. Until recently, the multi-dose HPV vaccine regimen has been recommended for children 11-12 years old, with catch-up or permissive immunization through age 26. However, the immunization rate of the HPV vaccine in the US is disappointing: overall, only 49% of adolescents (ages 13-17) are fully immunized.[5] In addition, although women who are poor or from racial or ethnic minority groups have disproportionately high rates of cervical cancer, their rates of HPV immunization are low. In October 2018, the FDA expanded the approved use of the HPV 9-valent vaccine to include mid-adult women and men 27-45 years of age. Given the low uptake in adolescents, sustained efforts for catch-up immunization are critical to address missed opportunities to protect adults against HPV-associated diseases.

Vaccination Post-Sexual Exposure

A commonly raised issue with vaccination of sexually active women is their likely prior exposure to HPV. Although vaccination is most effective before sexual exposure to HPV, vaccination of sexually active women remains highly effective and cost-effective. In an HPV vaccine efficacy trial with 18,644 women 15-25 years of age, including those who were sexually active, and average follow-up of 2.9 years, incidence of precancerous lesions of moderate grade 3 or worse (CIN2+) was 30% lower in the vaccinated arm.[6] There also were 24.7% fewer cervical excision procedures to treat precancerous lesions in vaccine recipients. Higher uptake of HPV vaccine could not only reduce the number of women that require surveillance and procedures to treat precancerous cervical lesions, which are linked to anxiety,[7] pain,[8] and adverse obstetrical outcomes,[9] but also reduce the associated medical costs estimated to be $8 billion dollars.[10,11] Natural infections produce low antibody titers but do not confer lifelong immunity.[10] Subsequent HPV vaccination with the same HPV type will indeed produce a robust immune response,[12] however it does not eliminate any cervical disease that is present at the time of vaccination. Additionally, sexual exposure to HPV typically is limited to one type, therefore the 9-valent vaccine will contain other types in which the patient had not been exposed previously.[13]

Postpartum HPV Vaccine Studies

One of the main reasons the HPV vaccine has had such poor compliance is lack of access to care.[14] Vulnerable women that would benefit most from the HPV vaccine are often otherwise healthy individuals with minimal interactions with the healthcare system. However, as most pregnant women receive some prenatal care, the postpartum period is ideal to educate and implement a HPV

vaccination. Prior studies demonstrate <15% of pregnant women received any doses of HPV vaccine and <8% completed the series.[15-18] Given this window of opportunity, a few investigators have implemented postpartum HPV vaccination at their institutions, and the Departments of Health in the states of New York and Washington recommend it for women who have not completed the series.[18,19] One of the first postpartum HPV vaccination studies enrolled a sample of 150 Hispanic women who tolerated the vaccination with few side effects and patients reported a high degree of satisfaction.[20] However, 30% of the women completed all 3 doses, 23% received two doses, and 41% received only one dose during hospitalization. Completion of the series of three HPV doses was a challenge. The second study, also done in Texas, used patient navigators who used multiple reminder methods (texting, mailed reminders, and phone calls) to increase completion rates. This study reported a 65% completion rate and 75% of postpartum women received at least one dose.[21] Future studies should determine the optimal method to ensure vaccine series completion while using minimal resources and existing staffing.

Two Dose Regimen for HPV Vaccination

A two-dose regimen includes administration of an inactivated vaccine with the first dose as the priming dose and the second distant dose resulting in consolidation of the immune response.[22] The second dose administered at 6-months to allow complete initial B cell response stimulation; affinity-matured B cells produce an amnestic response after booster, but affinity maturation takes at least four months to develop. Recent studies have demonstrated non-inferiority of HPV vaccination in a two-dose regimen in adolescents.[22] A two-dose regimen may be beneficial in older patients as well, especially those who have difficulty with follow up for multiple doses of a vaccine regimen, but this has not been studied.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures

Pilot, non-inferiority clinical trial using historical controls

Participants will have whole blood drawn at 0-months, 6- to 12-months, and one month after the second dose of the vaccine. The HPV vaccine will be administered at 0-months, 6- to 12-months, and two to five months after the second dose of the vaccine. Each blood draw will consist of 15 mL to measure HPV serologies and hormone levels.

Initial contact

- Eligible participants who are being seen for prenatal care during the 3rd trimester of pregnancy or inpatient postpartum care will be notified by their provider about this HPV vaccination study. The study coordinator will identify eligible participants through EPIC and notify the providers which of their patients are eligible for the study. Providers will notify study team members of their patient's interests either in-person or through referral cards. Referral cards will be scanned into Epic electronic medical records.
- After eligible participants have been referred by their provider, the research coordinator will thoroughly explain the study to the participant, give the participant a study information sheet, and answer any questions the participant might have.
- If the participant agrees to participate, the research coordinator will consent the participant and collect brief demographic and clinical information pertaining to the study. The consent may occur in person or through a video visit in the form of a telehealth visit. The consent process may occur either when the patient is still pregnant during prenatal care or after the delivery of a child while the patient is hospitalized.
- If the patient declines to participate, the reason for declining would be documented. For all patients who are being seen for prenatal care during the 3rd trimester of pregnancy or inpatient postpartum care, the research coordinator will do a chart review to collect data at

the end of the enrollment phase. This information is needed to compare demographic data between those who agree to participate in the trial and those who decline or were never approached.

Visit 1 (0-Months)

- After delivery of a live child, the enrolled participant will have 15mL of blood drawn and labelled with a unique study ID.A vial of the vaccine will be ordered from the Pharmacy and Investigational Drug Services (IDS) through EPIC and **dose #1** will be administered by a licensed medical provider per clinical protocol (e.g., intramuscular [deltoid]).
- After the vaccine is administered, the study coordinator will observe the participant for 15 minutes to note any untoward events or allergic reactions.
- The de-identified blood tube will be sent to the Hopkins laboratory for processing and storage until shipped at study end.

Visit 2 (6- to 12- Months)

- After the baseline visit (0-months), all follow-up visits will take place at an OB/GYN clinic or a CRU located at Johns Hopkins Hospital or Bayview.
- Participants will be contacted by the research team at 5-months using their preferred contact preference to schedule a 6-month research visit at an OB/GYN clinic or a CRU.
- If participants cannot come at 6-month for the second visit, the research team will contact them to schedule a research visit between 6 and 12 months.
- Participants will be asked for their last menstrual period date and provide 20mL of urine for a pregnancy test before proceeding with the study.
- If the pregnancy test is negative, participants will have 15mL of blood drawn and labelled with a unique study ID.
- A vial of the vaccine will be ordered from the Pharmacy and Investigational Drug Services (IDS) through EPIC and dose #2 will be administered by a licensed medical provider per clinical protocol (e.g., intramuscular [deltoid]).
- After the vaccine is administered, the study coordinator will observe the participant for 15 minutes to note any untoward events or allergic reactions.
- Participants will be scheduled for their visit 3.
- If the pregnancy test is positive, participants will be withdrawn from the study. Participants will be advised to contact their OB/GYN for further clinical management.

Visit 3 (One month after Visit 2)

- Participants will have their final blood draw of 15mL collected and labelled with a unique study ID.
- There is no vaccine administered at this visit.

Visit 4 (One to five months after Visit 3)

- At Visit 3, participants will be scheduled for a study visit during in one to six months that will take place at an OB/GYN clinic or a CRU located at Johns Hopkins Hospital or Bayview. This is the time for a routine gyn annual examination, and the vaccine can be administered during that visit as well.
- Participants will be asked for their last menstrual period date and to provide 20mL of urine for a pregnancy test before they can precede with the final vaccine dose.
- A vial of the vaccine will be ordered from the Pharmacy and Investigational Drug Services (IDS) through EPIC and dose #3 will be administered by a licensed medical provider per clinical protocol (e.g., intramuscular [deltoid]).

- After the vaccine is administered, the study coordinator will observe the participant for 15 minutes to note any untoward events or allergic reactions.
- There is no blood drawn at this visit.
- If the pregnancy test is positive, participants will be withdrawn from the study. Participants will be advised to contact their obgyn for further clinical management.

Home visits

Participants can choose home visits for visits 2 to 4 instead of coming into the clinic or CRU. We have a home visit team that includes at least two research staff members, and one of them is a registered nurse (RN). The RN will be responsible for the urine pregnancy test, blood draw, and vaccine injection. All these activities can be done safely in the home. Before and on the day of the home visit, participants will be screened for COVID symptoms. Up-to-date screening questions will be utilized to assess the risk of coronavirus transmission. In the home visit, the home visit team will follow the protocol as described above. The home visit team is equipped with emergency kits which include allergy and asthma medications. Because participants all received the first dose of the vaccine at the hospital without any allergic reactions, the risk of adverse events for the second and third doses of the vaccine is very low. If any adverse event were to happen, the team would immediately start emergency treatment following the American Red Cross Guidelines for anaphylaxis and the practice parameter developed by the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology. The emergency management includes assessing airway, breathing, and circulation, give intramuscular epinephrine, call 911, give inhaled beta2-agonist if bronchospasm is present, start CPR if needed, and inform the PI. However, these are very unlikely to happen because all the participants have a very low risk of severe adverse reactions to this vaccine when assessed at the enrollment and have received the first dose without any severe side effects.

b. If your study involves data/biospecimens from participants enrolled under other research studies with a written consent or under a waiver of consent, please list the IRB application numbers for those studies. Please note: Certificate of Confidentiality (CoC) protections applied to the data in source studies funded by NIH or CDC will extend to this new study if the funding was active in 2016. If this situation applies, Section 36, question 6 in the application will need to be answered "Yes" and "Hopkins Faculty" should be selected in question 7. No other documents are required.

N/A

c. Study duration and number of study visits required of research participants.

Study duration is two years. Each participant will undergo four study visits over 12 months on average. Two of the study visits can occur during routine clinical care.

d. Blinding, including justification for blinding or not blinding the trial, if applicable.

This is an open-label non-inferiority clinical trial and historical controls will be used.

e. Justification of why participants will not receive routine care or will have current therapy stopped.

N/A

f. Justification for inclusion of a placebo or non-treatment group.

This is a pilot, open-label non-inferiority clinical trial and historical controls will be used.

g. Definition of treatment failure or participant removal criteria.

Participants who suffer severe adverse events from the HPV vaccine or who become pregnant will be withdrawn from the study.

h. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Participants will resume routine clinical care.

i. If biological materials are involved, please describe all the experimental procedures and analyses in which they will be used.

The study site will adhere to standards of good laboratory practice and local standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens to the local laboratory and outside laboratories

JHH or Bayview Clinical Laboratory or ObGyn clinic

- POC Urine hCG Test (Pregnancy Test)
- Estrogen and Progesterone levels

JHU Research Laboratory

- Whole blood processing for serum and storage at –80^{o}C.

Specimens will be labeled with a unique study identifier (study number) instead of personal identifiers. Blood samples will be stored at a JHU research laboratory at –80^{o}C and shipped to a designed Merck laboratory at the end of the study.

Merck Laboratory

- Serum will be tested for vaccine HPV type antibodies by competitive Luminex immunoassay (cLIA). A participant will be defined as anti-HPV 6/11/16/18/31/33/45/52/58 positive if her anti-HPV serum level is $\geq$30, $\geq$16, $\geq$20, $\geq$24, $\geq$10, $\geq$8, $\geq$8, $\geq$8, or $\geq$8 milli Merck units (mMU)/mL for the 9 types, respectively. Assays to be performed by Merck's designee.

5. Inclusion/Exclusion Criteria

Inclusion Criteria

Participants biologically born as females between the ages of 15 through 45 who are willing to have the HPV vaccine at the hospital after delivering a live born baby.

Exclusion Criteria

Severe allergic reaction to vaccine components, prior receipt of an HPV vaccine dose, fetal demise or stillbirth, allergy to yeast, moderate or severe acute illness (deemed by the investigator to exclude), and immunosuppression (e.g., HIV, solid organ transplant).

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

GARDASIL 9 is an inactive HPV vaccine that is administered intramuscularly and available in 0.5mL single does vials. GARDASIL 9 is commercially approved by the FDA for the prevention of cervical, vulvar, vaginal, and anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58. Participants will receive the recommended FDA dosage throughout the course of the study.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Gardasil-9 is FDA approved as a 3-dose series for patients 15-45 years old, and as a 2-dose series for patients 9-14 years old. In a 3-dose series, the second dose is usually given 1–2 months after the first dose, and the third dose is usually given 6 months after the first dose (0, 1–2, 6 month schedule). Per the Centers for Disease Control and Prevention, there are minimal intervals for administration of the HPV vaccine but no maximum intervals.[23] The minimum intervals are 4 weeks between the first and second dose, 12 weeks between the second and third doses, and 5 months between the first and third doses. If a vaccine dose is administered after a shorter interval, it should be re-administered after another minimum interval has elapsed since the most recent dose. If the vaccination schedule is interrupted, vaccine doses do not need to be repeated (no maximum interval). To stay in compliance, all participants will still receive 3 doses of the vaccine, although the scheduling is different. We are allowing enough time between doses (minimal interval) to allow an appropriate B-cell response and participants will complete the series within one-year. Therefore, this study aligns with the lack of a maximum interval and poses no change in risk compared to the traditional dosing schedule.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

7. Study Statistics

a. Primary outcome variable.

- Anti-HPV16 antibody titers measured four weeks after the second dose.

b. **Secondary outcome variables**.

- Antibody titers to the other 8 HPV types
- Seropositivity for each HPV type after 1-dose and 2-doses
- Percentage of participants who complete 1-dose, 2-dose, or 3-dose vaccination
- Percentage of participants with baseline titers suggestive of natural infection or prior vaccination
- Characteristics and percentage of participants who completed study visits in-person using their own transportation, required Lyft, or requested a home-visit. Characteristics will include individual demographic characteristics, sexual reproductive health history, STI history, neighborhood median income based on zipcode and neigborhood deprivation index based on address.
- Thematic coding of field notes if home visits were conducted

c. **Statistical plan including sample size justification and interim data analysis**.

Geometric mean titer (GMT) ratios for each HPV genotype will be compared between the 2-dose and 3-dose regimen. As a non-inferiority trial, the primary analysis will use the per-protocol analysis. One-sided 90% confidence intervals (adjusted for multiple comparisons) will be constructed for the primary immunogenicity, which is the accepted method of reporting non-inferiority results. Antibody GMTs at month-7 (4 weeks after 2nd dose) among participants who received the 2-dose regimen will be compared with historical controls who received the 3-dose regimen.[24] The criteria for declaring non-inferiority will be defined as the lower bounds of the multiplicity-adjusted 90% CI for the ratio of antibody GMT greater than 0.67. This non-inferiority margin was selected based on bridging studies used for licensure.[25]

Table 1: Statistical Intervals[26]

Confidence Level	Sample Size (N)	Actual Distance from Mean to Limit	Standard Deviation (S)

0.900	107	0.125	1.000
0.900	107	0.150	1.200

Estimating the standard deviation of the GMT ratio to be 1.2 based on preliminary data, a sample size of 107 will produce a one-sided 90% confidence limit with a distance from the mean to the limit of 0.15. That is, if the GMT mean ratio is ≥ 0.82, we will be 90% confident that the true ratio is not less than 0.67. To allow for almost 28% attrition, we will enroll 231 subjects.

Secondary endpoints include % seropositive at baseline (before administration of 1st dose), % of participants who seroconverted. Descriptive statistics will be performed. Additionally, we will determine if hormone levels are associated with seropositivity and GMTs.

Given the success of our home visits as a method to increase retention, we would like to write a separate paper (brief report) to share our methodology with other researchers.

De-identified serum samples will be shipped to a Merck designated laboratory to perform the proprietary assay for HPV antibodies. No PHI will be shipped. Shipment will occur at study end in one batch. Hormone levels will be shipped to OHSU for analyses.

d. **Early stopping rules**.
Participants will be temporarily or permanently removed from the study regarding a severe AE related to the vaccination. Any participants with a positive pregnancy test after the baseline visit will be permanently removed from the study.

Participants may voluntarily withdraw from the study for any reason at any time. The PI may withdraw participants before their scheduled termination visit in order to protect their safety, and/or if participants are unable or unwilling to comply with study procedures. During the study, any abnormalities identified by history, physical examination, or laboratory tests will be reassessed until resolution, an explanation is found, or up until one month if changes are deemed permanent.

8. Risks

a. **Medical risks, listing all procedures, their major and minor risks and expected frequency.**
Risks of the proposed study include the risk of pain, infection, dizziness, swelling, bruising, or bleeding from the needle stick that can occur with phlebotomy. Risks commonly associated with venipuncture include bleeding, occasional bruising at the site of venipuncture, hematoma, or infection. Rare complications (1/100) include lightheadedness or fainting. Other risks include infection, damage to the vein, blood clot or stroke, if a large amount of air enter the vein, but these are rare. Early pregnancies may not be detected even with a known last menstrual period and urine pregnancy test. The vaccine is not a live virus and does not cause birth defects. Administration of the vaccine may cause injection site pain, injection site swelling, redness of the skin, allergic reactions, and/or headaches. The vaccine also has a small risk of syncope.

b. **Steps taken to minimize the risks.**
Only licensed medical staff will draw blood and administer the vaccine. Participants will be monitored after the vaccine to ensure there are no missed side effects. To minimize the chances of pregnancy, participants will be asked if they are using an effective form of birth control (e.g. pills, patch, ring, sterilization, implant, iud, same-sex relationship, abstinence), asked for the date of the last menstrual period, and undergo a urine pregnancy test.

c. Plan for reporting unanticipated problems or study deviations.
All adverse event and serious adverse events will be reported to the study PI and the Johns Hopkins University IRB. The PI or study coordinator may contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877- 888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov with any vaccine exposures during an early pregnancy.

d. Legal risks such as the risks that would be associated with breach of confidentiality.
Although the study site will make every effort to protect the privacy and confidentiality of all study volunteers, it is possible that volunteers' involvement in the study could become known to others. This risk is communicated to all research subjects in JHMIRB approved studies.

Given the sensitive nature of the proposed studies, the investigational team will keep the study information private to the extent possible by law. Where possible, clinical information will be identified by a unique number assigned to each individual research participant. Access to study records will be limited to the study team, including the Johns Hopkins University CRU staff involved in the study, the Office of Human Research Protections, and Johns Hopkins University officials, where applicable and required by law. Enrolled patients will be assigned study numbers for data collection and evaluation. Publications in medical journals arising from this study will not include any names or other identifiers of the subjects involved.

The key linking research subjects to study numbers will be kept as an electronic file. Electronic files will be maintained on the PI's SAFE Desktop with limited access by the study team. Any paper files are maintained in a locked cabinet located in PI's office, again, with limited access to study investigators.

e. Financial risks to the participants.
N/A

9. Benefits
There are not direct benefits to subjects who participant in this study, but the study has potential to provide key strategies to ensure completion of the HPV vaccine series among postpartum women.

10. Payment and Remuneration
Participants in the study will receive a total of $75 dollars. $25 will be dispensed at visit 2 and $50 will be dispensed at visit 3. For participants who park in a Hopkins parking garage for visit 2 and visit 3, we will give them a patient/visitor parking coupon that will cover the cost of their parking for that visit. For participants arriving via bus, we will give them a bus token to cover the cost of their transportation. For participants unable to travel to visit 2 or 3 through the previous two methods, we will use a Lyft concierge service to call them a ride to and from the visit.
The $25 and $50 compensation at visits 2 and 3, respectively, will be issued either through Venmo or a Visa gift card, depending on the participant's preference.

11. Costs
There is minimal no cost to the participant as vaccine costs are covered by grant funding.

12. Transfer of Materials
a. Will you **receive** biospecimens from an external entity for this research? [No].

b. Will you **transfer** biospecimens to an external entity as part of this research? [Yes]
If "Yes", please address each of the following:

1) Describe the nature of the research collaboration with the external entity and the rationale for the transfer. (Include an explanation of your intellectual contribution to the design of the research study, resulting data and sharing, and participation in the planned publications.)

This study was designed by the PI and received support from Merck & Co.. Merck laboratory is responsible for testing antibody GMTs for each HPV genotype and providing historical data for us to compare. This ensure the feasibility of this clinical trials. Our results will be shared with Merck as the foundation for potiential larger clinical trials. People who made significant contibutions and are qualified for the authoship will be listed as one of the co-authors in the planned publications.

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