Study Application (Version 1.38)

1.0 General Information

*Please enter the full title of your study::		
An open label study of IgG Fc glycan composition in human immunity		
***Please enter the study short title:**		
Fc glycan composition in human immunity * This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.		
Is this Study using Subject Management?		
(•) Yes ( ) No		

2.0 Add departments

2.1 List departments associated with this study:

Is Primary?	Department Name
(•)	**RUH** - Laboratory of Molecular Genetics and Immunology (Ravetch)
( )	**RUH** - Rockefeller University Hospital (RUH)

3.0 Assign key study personnel(KSP) access to the study

3.1 * Please add a Principal Investigator for the study:

Name	Role	Training Record
Wang, Taia, MD, PhD	**Principal Investigator**	View Training Record

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Name	Role	Training Record
Caskey, Marina F, M.D.	**Clinical- Co-Investigator**	View Training Record
Ravetch, Jeffrey, MD PhD	**Clinical- Co-Investigator**	View Training Record

B) Research Support Staff

Name	Role	Training Record

3.0 Assign key study personnel(KSP) access to the study

Colagreco, Joseph P, DNP, NP-BC	**Study Coordinator**	**View Training Record**

3.3 *Please add a Study Contact:

Name	Role	Training Record
Colagreco, Joseph P, DNP, NP-BC	**Study Contact**	**View Training Record**
Wang, Taia, MD, PhD	**Study Contact**	**View Training Record**

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

4.0 Rockefeller University Conflict of Interest

4.1 Investigator Financial Conflict of Interest All KSP must complete an annual certification of their Significant Financial Interest ("SFI") disclosures in the University's online Research Administration System at https://RAS.rockefeller.edu. Disclosures also must be updated in connection with new human subjects research protocols ("Research Certification"), and within 30 days of discovering or acquiring a new SFI. To avoid delays in the IRB review process, when prompted by an email from rascoi@rockefeller.edu requesting an updated Research Certification, KSP should click on the Research Certification link contained in that email notification, or go to https://RAS.rockefeller.edu, to (a) review and update his or her SFI disclosures or certify that he/she has no updates, as appropriate, and (b) indicate whether any of his/her SFI disclosures are reasonably related to the design, conduct, or reporting of the research protocol. If a KSP discloses a SFI that might constitute a conflict of interest with respect to the proposed protocol, he or she must e-mail a copy of the Lay Summary of the draft protocol to Teresa Solomon, Esq. (solomot@rockefeller.edu). Doing so will facilitate addressing COI issues in step with the development of the study protocol. Non-compliance or tardiness in making or updating COI disclosures will result in a delay in IRB review. Institutional Conflict of Interest:

As early as possible the PI (or a designee) preparing a clinical research protocol must review a list of entities in which The Rockefeller University has an Institutional Financial Interest at https://icoi.rockefeller.edu/account/login.php. If the proposed study involves any entity on that list, the PI (or designee) must notify Teresa Solomon, staff to the FCOI Committee, by e-mail solomot@rockefeller.edu and Sarah Schlesinger, Chair of the IRB, by email: schless@rockefeller.edu, provide the name(s) of the entities and a copy of the Lay Summary. Doing so will facilitate addressing institutional COI issues in step with the development of the study protocol. Failure to take steps to review and address potential institutional conflicts of interest will delay the IRB review process.

5.0 External Personnel

5.1 List external personnel who will be working on the study:

Name	Institution	Telephone	E-mail	Role
Maurice Policar, MD	Elmhurst hospital	(718) 334-4952	JONESM@nychhc.org	Consultant
Shiv Pillai, MD, M.P.H.	Massachusetts General Hospital	617-726-5619	pillai@helix.mgh.harvard.edu	Collaborator
Joseph R. Masci, MD	Elmhurst hospital	(718) 334-3446	JONESM@nychhc.org	Consultant
John Stone, MD, PhD	Massachhusetts General Hospital	617-643-5385	jhstone@partners.org	Collaborator

6.0 Delegation of Authority

6.1 Enter authorized activities for all Rockefeller University personnel named on the study.

Activity Codes:

1. Informed consent **
2. Inclusion / exclusion criteria
3. Medical/medication history *
4. Perform Physical Exam *

4a. Write / Sign LIP orders *

5. Skin assessments and photos
6. Study drug dispensing *
7. Study drug administration *
8. Study drug reconciliation
9. Study drug compliance
10. Administer study questionnaire(s)
11. Participant recruitment
12. Perform assays
13. Specimen / sample analysis
14. Lumbar puncture *
15. Femoral line placement *
16. Central line placement *
17. Insulin clamp procedure *
18. Leukapheresis *
19. Sigmoidoscopy *
20. Fat biopsy *
21. Skin biopsy *
22. Conduct sleep study
23. Diet design and preparation
24. Nutritional assessment and counseling
25. Addition of PABA to food
26. Data analysis
27. Data review
28. Data management
29. Maintain regulatory documents / files
30. Complete CRF's

Add up to three additional authorized activities specific to this study (do NOT add activities that have previously designated codes):

31:	
32:	
33:	

Activity Codes Continued:

34. Behavioral Testing
35. Bod Pod
36. Bone Marrow Aspiration *
37. Neuropsychological Testing *
38. Conduct Focus Group
39. Conduct Smell Study
40. Genetic Counseling *
41. Apply EEG Electrodes **
42. Olfactometer Test
43. Study Participant Teaching
44. Resting Energy Expenditure
45. Source Document Review & Correction
46. Medical Photography
47. See 4a
48. Adverse Event Assessment
49. Clinical Trial Registration
50. Study Support Drug Dispensary
51. Internal Monitoring
52. Randomization

Enter delegation of authority for Rockefeller University Key Study Personnel:

NOTE:

* Indicates procedures requiring the individual complete specific credentialing **BEFORE** the activity may be added to their delegated activities.

** Indicates procedures requiring the individual complete specific training **BEFORE** the activity may be added to their delegated activities.

Name	Title	Authorized Activities	Start Date	End Date

Wang, Taia, MD, PhD	PI	1, 11, 12,13, 26, 27, 28, 29, 30	01/09/2013	11/03/2022
Buckley, Noreen, M.S., APRN-BC	Clinician	1,2, 3, 4, 7, 11, 28, 29, 30	01/09/2013	05/01/2015
Hurley, Arlene, MA, ANP-BC, CCRC	Clinician	1, 2, 3, 4a, 7, 10, 11, 28, 29, 30, 45, 48	01/09/2013	10/13/2021
Caskey, Marina F, M.D.	Co-I	1, 2, 4a, 11, 12,13,26,27,28, 29, 30	01/10/2013	11/03/2022
Schlesinger, Sarah J, M.D.	Co-I	1, 2, 4, 11, 12,13,26,27,28, 29, 30	01/10/2013	07/06/2017
Ravetch, Jeffrey, MD PhD	Co-I	11, 12,13,26,27,28, 29, 30	01/10/2013	11/03/2022
Pack, Maggi, Ph. D	Co-I	11, 12,13,26,27,28, 29, 30	01/10/2013	10/21/2016
Rosenberg, Brad R, MD, PhD	Co-I	11, 12,13,26,27,28, 29, 30	01/10/2013	01/29/2014
Rice, Charles, Ph.D.	Co-I	11, 12,13,26,27,28, 29, 30	01/10/2013	01/29/2014
Hadrigan, Sonya, Nurse Practitioner	Clinician	1,2, 3, 4, 7, 11, 28, 29, 30	01/13/2015	05/01/2016
Breton, Gaelle, PhD	Co-I	12, 26	02/17/2015	10/21/2016
Nussenzweig, Michel Claudio, M.D., Ph.D.	Co-I	26, 27	02/17/2015	10/21/2016
Levin, Rebeka, BS	RN	1,2,3,7,10,11,28,29,30,31	03/02/2016	07/06/2017
Butler, Allison, MSN, FNP-BC	NP	1,2,3,4a,7,10,11,28,29,30,48	05/17/2016	11/21/2019
Millard, Katrina G, ANP	NP	1,2,3,4a,7,10,11,28,29,30,48	07/11/2016	11/21/2019
Eylers, Ellen, MPH, MSN, RN, CCRC	Coordinator	1,2,10, 11,27,28, 29,30,31	10/21/2016	11/01/2017

Enter delegation of authority for additional Rockefeller University Key Study Personnel:

Name	Title	Authorized Activities	Start Date	End Date
Brassil, Donna, MA, RN, CCRC	Facilitator	1,2,10,11,27,28,29,48	11/09/2017	10/13/2021
Colagreco, Joseph P, DNP, NP-BC	Study Coordinator	1,2,3,4a,7,10,11,28,29,30,45,48	11/21/2019	11/03/2022

Enter the authorized activities for External Personnel:

Name	Title	Authorized Activities	Start Date	End Date
No results found				

7.0 Study Description

7.1

Study Classification

Full Review

7.2

* Submission Request Category

Note: For each submission, please designate the level of review, or "Submission Request Category" you are requesting. When completing this field, please indicate the level of review you are requesting for the specific submission you are working on.
For example, if you are submitting an Expedited Amendment request to change the Key Study Personnel on your existing Full Board study, you should select "Expedited Review" in both the Amendment Submission Form and Study Application. The IRB will confirm an Expedited review of the Amendment submission is appropriate, and the overall study will remain classified as a full Board review. Please see the help bubble for guidance.

To submit a request for a Not Human Subjects research determination, please exit this form and select the "Not Human Subjects Research Determination" form under Create a New Study.

- ○ Exempt from Review
- ○ Exempt with Limited Review
- ○ Expedited Review
- ◉ Full Review

7.3 * **Lay Summary**
Please provide a summary of your study in lay language that is easily understood by a non-scientist. The summary should be no more than half a page (500 words or less) and should contain a clear statement of the rational for the study.

Please provide a summary of your study in lay language. The summary should be no more than a half page (500 words or less) and should contain a clear statement of the rationale for the study.

Antibodies are principle mediators of immunity against infections and they can also give rise to autoimmune and inflammatory diseases. Two functional domains make up an IgG antibody – the Fab domain binds to a specific target, while the Fc domain can interact with receptor molecules to activate a pro- or anti- inflammatory state. The Fc domain of IgGs contains a glycan that is variable in composition and its specific sugar components are an important determinant of the biologic activity of IgGs in both protective and pathologic immune responses. New disease treatments could be developed through purposeful manipulation of IgG Fc glycans, but there is currently little known about how Fc glycan composition is regulated. We plan to study this by evaluating whether vaccination or infection can cause changes in Fc glycan composition and, if so, whether signaling from helper T cells, age of the patient, and/or route of vaccine administration are determinants of specific modifications that are triggered by vaccination. Next, we will study effects that specific components within the Fc glycan have on immunity against the common human pathogens *Streptococcus pneumoniae* and influenza viruses using *in vitro* and *in vivo* models of infection.

7.4

*** Public Health Impact Statement**

Provide a brief plain language statement (100 words or less) of the value of the research proposed and its potential impact on population health. Additional instructions located in Help.

In order to produce better more effective vaccines, it is important to understand the particulars of why individuals have an effective or ineffective immune response to vaccination. We are going to examine specific aspects of the antibody (IgG Fc glycan) made by healthy volunteers who receive different vaccines or who have a viral infection to understand the nature of an effective (or less effective) vaccine response. The results of this research could be used to develop adjuvants to increase/ improve vaccine response.

8.0

Clinical Trial Registration

8.1

Clinical Trial Registration

The types of studies listed below must be registered at **Clinical Trials website** before enrolling the first participant in order to be in compliance with federal regulations and preserve the opportunity to publish the study in journals that adhere to the **ICMJE guidelines**. Please check the answer that best applies.

- ○ Study involves testing of FDA regulated drugs or biologics (See HELP)
- ○ Study is funded by the NIH, and meets the definition of a "clinical trial" (see HELP)
- ◉ Study meets the ICMJE definition of a "clinical trial" (See HELP)
- ○ Additional funding agency or journal requires clinical trial registration
- ○ None of the above

If you selected 1, 2, 3, or 4 you must register your trial with ClinicalTrials.gov through the Rockefeller University institutional account. Please contact the Clinical Research Support Office x7408 for assistance.

9.0

Study Overview/Summary

9.1 *** Who initiated this study?**

Please specify one:

- (●) Principal Investigator Initiated
- ( ) Industry Initiated
- ( ) Other

9.2 *Are other institutions involved in the study?

- (●) No
- ( ) Yes

9.3 * Is this a multi-site trial using a single IRB (sIRB) review arrangement? Please see help bubble for definition.

- ( ) Yes (●) No

9.4 * Who (What) is to be studied?

- [x] Human Subjects - including coded samples and/or data with links to Identifiers
- [x] Deidentified Samples - unable to be linked to identifiers by receiver
- [ ] Data Only - unable to be linked to identifiers
- [ ] Identifiable samples or data for exemptions (per 104 (s)(4))

9.5 *Study Type:

- (●) Interventional
- ( ) Observational

9.6 The initial date of IRB approval/determination was:

02/07/2013

9.7 * What is the expected duration of the study?

10 years

9.8 * Are any of the following agents to be used in the study?

Check all that apply:

- [ ] FDA Approved Drug
- [ ] FDA Approved Drug for Off-Label Purpose (This might require an IND)
- [ ] Investigational New Drug
- [ ] Biologic Agents
- [ ] Nutritional Supplements
- [ ] Placebo
- [x] Vaccines
- [ ] No Agents
- [ ] FDA Exemption to use Study Drug

9.9 * Are investigational devices to be used in the study?

- ( ) Yes (•) No

9.15 Special Research Procedures

Does the study propose to directly involve participants in the following special research procedures?

- [ ] Recombinant DNA
- [ ] Gene Therapy
- [ ] Fetal Tissue
- [ ] Embryonic Stem Cells
- [ ] Induced Pluripotent Stem Cells
- [ ] CRISPR-Cas9

If any item is checked, please see Help for details.

9.16 * Radioactive Isotopes Involved

Will participants be exposed to any radiation other than routine x-rays solely for clinical care purposes?

- ( ) Yes (•) No

10.0 Interventional

10.1 *Interventional, please specify:

- (•) Open Label
- ( ) Single Blind
- ( ) Double Blind
- ( ) Other

11.0 Study Phase:

11.1 Study Phase:

Select where applicable

- ○ Phase 0
- ○ Phase I
- ○ Phase I/II
- ○ Phase II
- ○ Phase III
- ○ Phase IA
- ○ Phase IB
- ○ Phase IIA
- ○ Phase IIB
- ○ Phase IB/IIA
- ○ Phase IIB/IIIA
- ○ Phase IIIA
- ○ Phase IIIB
- ○ N/A

12.0 Objectives and Rationale

12.1 * Overview

Briefly state the ***purpose of this study***. Give enough background and rationale to provide both scientists and lay members of the IRB and ACCTS with the basis for exposing human participants to the risks involved.

Antibodies represent an important link between the adaptive and innate immune systems. IgG antibodies are bifunctional molecules comprised of a Fab domain, which determines binding specificity through the variable region, and an Fc domain, which interacts with a variety of receptors on immune cells to confer effector function to IgG molecules. These effector functions include positive regulatory mechanisms such as the activation of antibody-dependent cellular cytotoxicity (ADCC), phagocytosis, and pro-inflammatory cytokine production, as well as negative regulatory functions, such as inhibition of inflammatory immune responses. Effector functions are conferred via the Fc domain through specific amino acid residues in the Fc and the precise glycan composition of an N-linked, complex, biantennary glycan that regulates interactions with members of the IgG Fc receptor (FcR) family and the DC-SIGN family of molecules (**1**, **2**).

The Fc glycan is a powerful regulator of antibody effector function and its specific composition can determine whether an antibody has pro- or anti-inflammatory activity *in vivo* (**3-6**). For example, the presence of terminal sialic acid on the Fc glycan converts IgGs to anti-inflammatory molecules in a variable region-independent manner. This is exemplified in studies demonstrating that the therapeutic, anti-inflammatory activity of intravenous immunoglobulin (IVIG) is conferred solely through the fraction of IVIG containing Fc glycans terminating in sialic acid, which have been shown to interact with SIGN molecules expressed by innate immune cells (**4**, **7**). Similarly, the presence or absence of a branching fucose moiety modulates the interaction of the IgG Fc with activating Fc receptors to enhance or inhibit IgG mediated cellular cytotoxicity (**6**, **8**, **9**).

Though the precise saccharide composition of Fc glycans is known to be a significant determinant of the biologic activity of IgGs, little is known about how the composition is regulated or about the biological consequences of specific modifications. Interestingly, it has been observed in mice and in humans that exposure to immunogens can result in various modifications of the IgG glycan (**4**, **10**). We plan to study this phenomenon using seven different FDA-approved vaccines; by characterizing Fc glycans in pre- and post- immunization sera, we will define the type of antigen(s) that can elicit changes in Fc glycan composition in humans. We will also study whether healthy adults who have been previously infected with a flavivirus or alphavirus (dengue, zika or chikungunya) generate distinct Fc glycoforms after vaccination compared with healthy adults who have not had known infection with dengue, zika or chikungunya virus infection; for this study we will use the seasonal inactivated influenza vaccine because influenza reagents for analysis of the TIV-elicited IgGs are abundant and readily available.

We will also use existing serum samples from controlled influenza virus infection studies performed at the NIAID in order to study how specific Fc glycoforms on influenza-specific IgGs may change during infection and to compare Fc glycan modulations that may occur during infection with those elicited by vaccination. In addition, we will use existing serum samples from a study performed at Emory University. These samples were drawn from patients with dengue virus infection, during acute infection, following defervescence and 1-2 months post infection. We will use these samples to study how Fc glycoforms on dengue envelope protein-specific IgGs may change during infection and we will compare any changes with those observed on IgGs from patients with influenza virus infection.

That antigen exposure can modify Fc glycan composition suggests a possible role for cognate B cell - T cell interactions in the regulation of glycan composition. Accordingly, a second phase of this study will investigate whether T cell help is required for vaccine-elicited glycan modification. We will study this by comparing serum IgG Fc glycan profiles in volunteers who were vaccinated with either T cell dependent (TD) or T cell independent (TI) vaccine antigens. We will also evaluate whether the age of the patient or route of vaccine administration are determinants of vaccine-elicited glycan modification. Finally, we plan to study how specific IgG glycan modifications regulate immunity against *Streptococcus pneumoniae* and against influenza viruses in *in vitro* and *in vivo* models of infection.

12.4 * Engaging Stakeholders: Describe any plans to engage other stakeholders (Scientists, practitioners, patients, advocacy groups, etc.) for hypothesis generation, or feasibility purposes.

The Principal Investigator as well as other members of the Ravetch laboratory were involved in the hypothesis generation and the feasibility purposes of this application.

12.5 * Hypothesis

Describe the ***research hypothesis*** in a single sentence.

The saccharide composition of human IgG Fc glycans determines effector function of pathogen-specific IgGs during infection and may be distinct in people with prior symptomatic flavivirus or alphavirus infection, can be modulated by exposure to specific types of vaccine antigens or modulated during viral infection.

12.6 * Aim(s)

Indicate how you will ***address the hypothesis*** (e.g., to compare groups, to estimate a parameter, to ascertain feasibility). Since the sample size determination is usually based on the primary aim only, the primary aim should be sufficient to justify the study.

Aim 1:
To determine whether vaccination can elicit modifications in Fc glycan composition and, if so, whether the T cell dependence of a vaccine antigen, age of the patient at vaccination or route of vaccine exposure regulate observed modifications in the IgG Fc glycan.

Aim 2:
To determine how specific components of the IgG Fc glycan regulate immunity against influenza viruses and against *Streptococcus pneumoniae* in *in vitro* and *in vivo* models of infection.

Aim 3:
To determine whether infection with influenza virus or dengue virus infection can elicit modifications in Fc glycan composition and to compare any changes with those observed following vaccination.

Aim 4:
To determine whether people who develop clinically significant flavivirus or alphavirus (dengue, zika or chikungunya) infection produce distinct Fc glycans in response to vaccination.

Aim 5:
To determine the Fc glycosylation status and in vivo activity of IgG4 antibodies from patients with IgG4 diseases

12.7 * Primary Outcome(s)

Indicate which ***variable(s)*** will be assessed to judge the primary specific aim. Give measurement units, if applicable.

Determination of saccharide components of the IgG Fc glycan pre- (day 0) and post- (day 7 and day 21) vaccination with different vaccines and before, during and following influenza virus infection:

- The degree of galactosylation, fucosylation and sialylation of pre- vs. post- vaccination Fcs determined by lectin blot (*Erythrina cristagalli, Aleuria Aurantia Lectin* and *Sambucus nigra* lectins specific for galactose, fucose and 2,6-sialic acid, respectively).
- Characterization of glycan composition by mass spec analysis.

Determination of the role of route of antigen exposure, age of the patient, or past flavivirus or alphavirus infection in regulation of Fc glycan modifications.
- Using three influenza virus vaccines (two inactivated that are administered either intramuscularly or intradermally, and one live that is administered intranasally) we will compare how the route of administration affects modifications of the Fc glycan by western blot and mass spec analysis.
- By comparing vaccine responses in patients < 65 or ≥65 of years of age we will determine how age regulates post-vaccination modifications of the Fc glycan.

12.8 * Secondary Outcome(s)

Indicate which ***additional variable(s)*** will be assessed to judge the secondary outcome(s). Give measurement units, if applicable.

Characterization of effector function of pathogen-specific IgGs during infection as a function of Fc glycan composition:
- The IgG subclass distribution will be determined using data resulting from the mass spec analysis performed for the primary study outcome.
- *In vitro* analysis of antibody dependent cell cytotoxicity and antibody dependent cellular phagocytosis mediatedby anti-influenza IgG with different Fc glycan profiles.
- *In vitro* analysis of cellular maturation and function using PBMCs from study participants.
- Analysis of gene expression using PBMCs from study participants.
- *In vivo* analysis of protection mediated by anti-influenza or anti-pneumococcal IgG with different Fc glycan composition in murine influenza virus or pneumococcal models of infection.

12.9 * Methods and Procedures

Please provide a description of the laboratory and clinical analyses and procedures that will be performed. Include the role of external collaborators and consultants when appropriate. Please refer to Help text for Guidance.

Study Design:
The study population consists of healthy volunteers between the ages of 18 and 80.

215 volunteers who meet all the eligibility criteria will be enrolled in this study.

The study is divided into 3 arms. The groups are defined as follows:

Arm I: Age 18-64 group: Groups of 10 study participants each (except for group 2 which includes 25 participants) < 65 years of age (< 50 years of age for Flumist vaccine and < 55 years of age for meningococcal vaccines) will be **vaccinated with one of seven FDA approved vaccines (85 participants total): Group 1)** Fluzone intradermal influenza virus vaccine, **Group 2)** Fluzone intramuscular influenza virus vaccine, **Group 3)** Pneumovax 23 (plain polysaccharide pneumococcal vaccine), **Group 4)** Prevnar/PCV13 (pneumococcal conjugate vaccine), **Group 5)** MPSV4 (plain polysaccharide meningococcal vaccine), **Group 6)** Menveo (meningococcal conjugate vaccine), **Group 10)** Flumist Quadrivalent (intranasal influenza live vaccine).

Arm II: Age 65-80 group: Groups of 10 study participants ≥65 years of age will be **vaccinated with one of three of the FDA approved vaccines (30 participants total): Group 7)** Fluzone intramuscular influenza virus vaccine, **Group 8)** Pneumovax 23, **Group 9)** Prevnar. Meningococcal vaccines, the intradermal influenza vaccine and intranasal Flumist will not be administered to participants in Arm II.

Arm III: Healthy adults, age 18-80, with a specific medical history as described here and in Section 12.11 (Inclusion Criteria): Groups of 25 study participants will be vaccinated with the Fluzone intramuscular influenza virus vaccine (100 participants total). **Group 11)** Prior diagnosis of dengue fever or dengue virus infection. **Group 12)** Prior diagnosis of dengue hemorrhagic fever. **Group 13)** Prior diagnosis of chikungunya virus infection. **Group 14)** Prior diagnosis of zika virus infection

The study will occur in four phases:
Phase 1: Volunteers will be recruited to receive influenza vaccines (Groups 1, 2, 7, 10). Recruitment for Groups 1 and 7 will occur simultaneously and volunteers will be enrolled sequentially - enrollment into Group 1 will be given priority over Group 2 because the intradermal vaccine preparation for the 2012-13 influenza season will expire earlier than the intramuscular preparation (April 2013 vs. June 2013). Volunteers will be recruited to receive the Flumist influenza vaccine (Group 10) beginning fall of 2013.

Phase 2: Volunteers will be recruited to receive one of the pneumococcal vaccines (Groups 3, 4, 8, 9) - these subjects will be recruited simultaneously and will be randomized to receive either the Pneumovax or Prevnar vaccines.

Phase 3: Volunteers will be recruited to receive one of the meningococcal vaccines (Groups 5 and 6) - these subjects will be recruited simultaneously and will be randomized to receive either the MPSV4 or Menveo vaccines.

Phase 4: Volunteers will be recruited for Arm III of the study to receive the Fluzone intramuscular vaccine (Groups 11-14)

Study participants will not be blinded. During the analysis phase, samples will be coded so that the precise vaccine administered within each phase is unknown.

Study visits will be scheduled as follows for groups 1-10: screening, day 0 (within 4 weeks of screen), day 7 safety visit, and weeks 3, 5, 7, 9, and 12. On Day 3-4, a telephone call will be made to check on subject's medical status.
Groups 11-14 will be scheduled as follows: day 0 (within 4 weeks of screen), day 7 safety visit, and week 3. We will not collect samples at weeks 5,7,9 or 12 for Groups 11-14 because our existing data on intramuscular Fluzone immunization from Group 2 demonstrate that the major Fc glycan modifications occur during the first 3 weeks following vaccination.

We do not anticipate any safety issues related to this protocol as all vaccines to be used have been FDA approved and all study participants are healthy adults.

Protocol Timeline
See Study Design groups 1-10 in other study documents
See Study Design groups 11-14 in other study documents

Subjects in Groups 1 and 2 (Fluzone ID < 65 years of age and Fluzone IM < 65 years of age) will be asked to return to the clinic for an additional study visit between 6 and 12 months from their Day of Vaccination (Day 0). This visit will include vital signs, any updates to their medical/vaccination history, as well as a blood draw of 23.5 ml for sera and PBMCs. The rationale to include this additional timepoint is that our data from subjects who received the 2012-13 Fluzone vaccines show modulations in Fc glycan composition on antigen-specific IgGs post vaccination; the Fc glycans change over time following vaccination, but are not at baseline composition by the 12 week timepoint (the latest timepoint) in our study. Inclusion of the 6-12 month timepoint in the Fluzone study groups will enable better characterization of the kinetics of Fc glycan changes, which is important since the modifications are likely to augment IgG effector functions. We will collect a detailed history of any vaccinations or illnesses occurring since the last study visit in order to incorporate the information into our analysis. Sera collected at this late timepoint will enable analysis of Fc glyan composition and PBMCs will enable analysis of vaccine-specific B and T cell functioning.

Screening Procedure and Study Visits
Potential participants will first undergo pre-screening by telephone to assess medical history and qualification for the study. Potential volunteers will have the opportunity to discuss the study and ask questions of the study recruiter at this time. Those who are eligible and interested in participation will attend a screening visit at the Rockefeller Hospital Outpatient Clinic.

Screening Visit: Study personnel will answer any questions about the study. Written informed consent will be obtained prior to conducting any study procedures. To ensure informed consent, the principal investigator or designee will discuss the following processes and explanations individually with each volunteer:

1. Pre HIV-test counseling;
2. Risk-reduction counseling including safe-sex and pregnancy avoidance counseling;
3. That a sexually active volunteer should use a reliable form of contraception throughout the study.
4. For Arm III, study personnel will request authorization from the participant to obtain their medical records as possible and/or speak to the treating provider from the time of virus infection. Participants will be asked to sign the HIPPA Compliant Authorization for Release of Medical Information.

If the volunteer consents to participate, site personnel will:

- Perform complete medical history (including concomitant medication);
- Perform a general physical examination including height, weight, vital signs (pulse, respiratory rate, blood pressure and temperature), examination of skin, respiratory, cardiovascular and abdominal systems, and an assessment of cervical and axillary lymph nodes;
- Safety labs will be drawn (WBC with differential, RBC, hemoglobin/hematocrit, platelets, Na, K, Cl, CO2, bun/creatinine, glucose, total and direct bilirubins, alkaline phosphatase, AST, ALT and urinalysis), as well as serologies -Hep BsAg and HCV for all Groups, for Groups 11-14 additional serologies will be performed for dengue and chikungunya viruses to ensure eligibility and vaccine safety. Rapid point of care (POC) saliva test will be performed to test for HIV.
- Perform a pregnancy test for all female volunteers;

Day 0, Vaccination Visit: Prior to vaccination, site personnel will:

- Answer any questions about the study;
- Review interim medical history (including concomitant medications);
- Review safety laboratory data;
- Review the informed consent form administered at screening visit with volunteer;
- Perform a physical examination including vital signs (pulse, respiratory rate, blood pressure and temperature), examination of skin, respiratory, cardiovascular and abdominal systems, and an assessment of cervical and axillary lymph nodes;as well as an assessment of axillary lymph nodes and any further examination indicated by history or observation;
- Risk-reduction counseling including safe-sex and pregnancy avoidance counseling;
- Safety labs will also be drawn prior to vaccination.
- Research bloods (81mL) will be drawn.
- Perform a point of care pregnancy test for all female volunteers and obtain results prior to vaccination;
- Perform baseline assessment of the site of injection and evaluate and record any systemic symptoms;
- Each participant will then receive a vaccination with one of the seven FDA approved vaccines. Participants will be monitored in the clinic for any vaccination reactions. Vital signs will be performed pre and post vaccination.
- Presence or absence of local and/or systemic reactogenicity events, as well as any other event that occurs, will be recorded post vaccination.

Day 7:

- Safety labs will be drawn.
- Research bloods (81mL) will be drawn.
- A targeted physical examination including vital signs (pulse, respiratory rate, blood pressure and temperature), as well as an assessment of axillary lymph nodes and any further examination indicated by history or observation will be performed.
- Perform a point of care pregnancy test for all female volunteers.

Weeks 3, 5, 7, 9, 12:

- Vital signs (pulse, respiratory rate, blood pressure and temperature) will be taken.
- Research bloods (20-170mL) will be drawn.
- Perform a point of care pregnancy test for all female volunteers.
- Groups 11-14 will not have bleeds done at week 5,7,9,12 or thereafter.

During follow up visits at day 7 and weeks 3, 5, 7, 9 and 12, study participants will receive pregnancy testing prior to sample collection because pregnancy is known to alter Fc glycan composition and would thus significantly confound study results. Volunteers with positive pregnancy tests will be discontinued from further participation in the study.

Withdrawal from the study (Early Termination)
Volunteers may be withdrawn from the study permanently for the following reasons:

1. Volunteers may withdraw from the study at any time if they wish to do so, for any reason.
2. Following an adverse event at the discretion of the investigator (or designee).

Blood Collection
Venous blood will be collected at study visits, usually from the antecubital fossa. Up to 20-170mL will be collected at study visits. At no time will the total volume of blood collected exceed 550 mL over an 8-week period. The total blood volume over the 12 week study period is 615mL. The volume of blood was increased to 615mL to conduct exploratory studies that are indicated by preliminary data from the influenza virus vaccine cohort. We have seen that there are modifications in IgG Fc glycan content induced by vaccination and that glycan composition may correlate with the avidity of vaccine-elicited IgGs. As a follow-up to these observations, we will evaluate how specific glycan modifications may correlate with activation and function of a variety of different peripheral blood cell types, some of which are found in extremely low frequency, such as DCs and CD4 follicular T helper cells. These studies will require PBMCs from an additional 80mL of blood at each of three time points in the study timeline: baseline, day 7 and week 3. This is now reflected in the total blood volume of 615mL. All specimens will be handled and processed in the GLP Processing Lab of the Laboratory of Cellular Physiology and Immunology. Only a code number will identify the samples. Frozen PBMCs, plasma and serum will be stored at RU.

Reimbursement
Volunteers will be compensated $75 for their vaccine visit, $35 for the follow-up blood draw visits except for the final visit, for which participants will be compensated $75. Reimbursement will be outlined in the informed consent form.

It is expected that volunteers for Arm III will be more likely to live outside of the immediate area, as patients with prior flavivirus or alphavirus infection are relatively rare. In consideration of anticipated

travel time for volunteers in Arm 3, participants will receive $25 for the screening visit, and compensation will be a minimum of $100 for each visit.

Sample preparation and laboratory analysis
Leukocytes will be separated from plasma, red blood cells and platelets by Ficoll (GE) gradient centrifugation. Plasma, serum and cells will be frozen for analysis at a later time. The serum will be characterized for cytokines using luminex multiplex assays and ELISAs. Serum will also be used to extract IgGs for analysis by ELISA, western blot and by mass spec for specificity and Fc glycan content. Fc glycans will be analyzed following isolation of antigen-specific IgGs by affinity chromatography. Vaccine preparations or purified proteins/polysaccharides will be coupled to sepharose beads as previously described for extraction of specific serum IgGs (**11-14**). Fc glycans from antigen-specific IgGs will be isolated by digestion with EndoS enzyme for subsequent mass spec analysis of the Fc glycan (**15**). Vaccine preparations for research use will be obtained from the RU pharmacy, purified influenza virus antigens will be obtained from the Biodefense and Emerging Infections Research Resources Repository, purified pneumococcal polysaccharides from ATCC. Serum IgGs will also be used in in vitro and in vivo (murine) assays in the laboratory to assess the functional consequence of Fc glycan modifications during infection with influenza viruses or with Streptococcus pneumonia (**16-18**). Mice humanized for FcgRs will be used for in vivo studies using human IgGs (**19**). RNA will be extracted from samples collected in PAXgene tubes for analysis related to specific modifications of IgG Fc glycans occuring post-vaccination.

In addition to the above samples, we will study existing serum samples from a study performed at NIAID in which healthy volunteers were infected with influenza virus in a controlled hospital setting. Samples will be obtained from an exiting collection from approximately 30 study participants from the following time points: pre-infection, day 3 post infection, day 7 post infection, week 3 post infection and week 5 post infection (for a total of 150 samples). Subjects in the infection study performed at NIAID consented to future use of samples for scientific investigation and samples will be de-identified without any accompanying information containing patient identifiers. Laboratory analysis of the serum samples will follow the same protocol as described above for sera collected under the vaccination protocol. Investigators from the NIAID will not be collaborating on this research; they will not be receiving any data derived from this study, will not participate in data analysis, and will not co-author any publications stemming from this study.

In addition to the above samples, we will study existing serum samples from a study performed through Emory University in which patients with diagnosed dengue virus infection had blood drawn. Samples will be obtained from an existing collection from approximately 10 study participants from the following time points: acute infection, post-defervesence, and 1-2 months post-infection. Subjects in this study consented to future use of samples for scientific investigation and samples will be de-identified without any accompanying information containing patient identifiers. Laboratory analysis of the serum samples will follow the same protocol as described above for sera collected under the vaccination protocol. Investigators from Emory will not be collaborating on this research; they will not be receiving any data derived from this study, will not participate in data analysis, and will not co-author any publications stemming from this study.

With the August 2018 amendment, de-identified research samples (serum) will be received from collabrators from the Massachusetts Genral Hospital (Pillai and Stone) obtained from patients with IgG4 related diseases. A total of approximately 20 research samples will be received in the Ravetch laboratory. There will be no attempt on the part of the Principal Investigator at the Rockefeller University to link the identity of the participant to the research sample nor will the collaborators at Massachusetts General Hospital provide the code to the identity of the participant sample. The MGH collaborators will receive the data derived from this study as it relates to their research samples as needed.

12.10 * Data Analysis

Describe method(s) of data analysis.

In order to find evidence that IgG Fc glycan composition changes from pre- to post-vaccination, we will apply two-sided t-tests and wilcoxon

tests for paired samples with significance fixed at 5% when evaluating change in abundance of specific saccharide units. For each vaccine antigen, we will be comparing pre- (day 0) to post- (day 21) vaccination IgG Fc glycan composition in order to see which vaccines elicit significant saccharide modifications. We will apply the same analysis to data obtained through study of samples taken prior to and at day 21 post influenza virus infection. For the analysis of the time course experiment and comparison across different groups, we are going to use Repeated Measures ANOVA, descriptive graphics and possibly fitted curves that may bring information about changes in time. Depending upon results in humans (Aims 1 and 2), in vivo experiments will be carried out in mice. For this stage, our Biostatistical Core will be consulted about the appropriate design and analysis of the experiments.

12.11 * **Explain the rationale for the choice of statistical measures and the number of participants proposed for the study, including the power calculations when applicable.**

Sample size evaluation was carried out to provide 80% power and 5% of significance for a two-tailed paired t-test to verify pre-post differences in the relative abundance of sugars. For each one of the specific saccharides to be measured, we expect an effect size a 10% change in relative abundance, with a standard deviation of 4.4% - this is based on data presented in Selman et al. (2012). Selman et al. evaluated changes in IgG1 Fc saccharide abundances (galactosylation, fucosylation and sialyation) following influenza vaccination of 10 Caucasian adults. Based on their data, we selected the highest standard deviation, which occured in abundance of sialyation. Adjustments for error multiplicity were done by a Bonferroni-Correction that reduced the individual significance levels to be 0.017 (0.05 significance divided by 3 sugars evaluated). Another adopted measure for taking into account the uncertainty about the standard deviation was to inflate that estimate by multiplying it by 1.30. This caused our standard deviation to increase to 5.72% from 4.4%. After all described procedures, using the function *n.ttest* in package *samplesize* in R, the initial evaluated sample size resulted in n=7 per group. It is important to emphasize that only samples from subjects with a two-fold increase in vaccine-specific antibody titer will be further analyzed for IgG Fc glycan saccharide composition. Thus, the evaluated sample size was increased to n=10 to accommodate the possibility of having a 20% rate of vaccine non-responsiveness and also the expected rate of volunteer drop-off (10%).

ARM III: We have preliminary data on the abundance of afucosylated glycans on anti-dengue envelope protein IgG from patients with acute dengue virus infection- the data are from one time point (acute infection) and we are comparing two groups: patients with dengue hemorrhagic fever (the severe disease) vs. dengue fever (the mild form of the disease). The maximum coefficient of variation between the two groups was 55%. Assuming that for the present study the populations to be sampled will have the same variability, a sample size of n = 25 (per group) would guarantee 80% power at 5% significance to detect a minimum Fold-Change (FCH) of 1.5 (50% increase) when comparing two independent groups with an unpaired two-sided t-test. In this calculation, we are taking into account that 5 pairwise comparisons will be performed, thus the test-wise significance level will be reduced to 0.01.

12.12 * **Will samples be coded?**

(•) Yes ( ) No

If Yes, Please describe coding scheme consistent with GCP. If samples will not be coded, please provide justification for this proposed departure from GCP practice.

The blood samples for all volunteers will be coded using the IRB approval number, date, and subject number, e.g. TWA-0804-001. The subject codes will be maintained in a password-protected database

on a RUH backed-up computer in the Ravetch lab that is accessed only by the Principal Investigator and the reseach team.

Once the samples are processed, the plasma will be stored in a -80C freezer in the Ravetch lab until time of assay.

If available, upload the Data and Sample Sharing Management Plan approved by RU IT.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document

No Document(s) have been attached to this form.

13.0 Participants of Study

13.1 Specify age range of participants:

* Minimum Age:

18

* Maximum Age:

80

Please note: If the age of participants indicated is less than 18 years old, you will be prompted to attach a Pediatric Assent form later on in the submission process. A link to the Pediatric Assent form can be found in the Help link to the right, or this form can be downloaded later on in the submission process.

13.2 * Indicate the gender(s) of the participants:

- [x] Female
- [x] Male
- [ ] Unknown
- [ ] Not Reported

13.3 * Indicate projected enrollment by race and ethnicity. See Help for disease/volunteer population demographics.

Ethnic Category	Sex/Gender			
	Females	Males	Unknown or Not Reported	Total
Hispanic or Latino	31	28	0	59
Not Hispanic or Latino	82	74	0	156
Unknown (individuals not reporting ethnicity)	0	0	0	0
Ethnic Category: Total of All Subjects*	113	102	0	215
Racial Categories				
American Indian/Alaska Native	0	0	0	0

Asian	14	12	0	26
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	38	33	0	71
White	61	57	0	118
More Than One Race	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of All Subjects*	113	102	0	215

13.4 Exclusion of Protected Groups:

***Research involving human participants should be designed/conducted to be as broadly inclusive as possible regarding sex, gender, race, age, and ethnicity. Exclusions regarding these characteristics require an explanation of the rationale and justification.**

Will participants of a specific sex/gender/race/ethnicity/age or other protected group characteristic be excluded from participation?

○ Yes ◉ No

13.5 Vulnerable Populations

Indicate whether any of the following populations will be included in the study:

☐ Children
☐ Pregnant Women
☐ Cognitively Impaired Persons
☑ RU Employees
☑ RU Students
☐ Other:

If you checked any of the above, give a brief explanation of the need to use these particular individuals:

RU employees and students will be enrolled if they meet study eligibility. Special precautions will be used in recruiting employees and students of the Rockefeller University to minimize the possibility of undue influence. Rockefeller University employees will be made aware of the study through flyers rather than directed presentations to selected groups. Subjects will be reassured that refusal to participate in the study will not affect their studies or employment in any way and that all medical records will be kept in accordance with HIPAA guidelines to ensure privacy.

If the participant is a Rockefeller University employee, does she/he work within the Laboratory of the Principal Investigator or Co-Investigator(s)?

◉ Yes
○ No
○ N/A

If the participant is a Rockefeller University student, does she/he work within the Laboratory of the Principal Investigator or Co-Investigator(s)?

◉ Yes
○ No

N/A

13.6 ***What is the total number of <u>evaluable</u> participants you plan to enroll at Rockefeller University Hospital over the course of the entire study?**

215

13.7 ***** **What is the total number of participants who will need to sign consent *at Rockefeller University Hospital over the course of the entire study* to result in the desired number of evaluable participants?**

278

13.8 ***** **What is the total number of participants you plan to sign consent *at Rockefeller University Hospital in the next year?***

20

13.9 ***** **What will be the total number of evaluable participants *at all sites over the course of the entire study?***

215

13.10 Inclusion Criteria

Please list participant inclusion criteria:

Order Number	Criteria
1	• Male or Female 18-80 years of age
2	• Healthy volunteers without significant medical problems
3	• Able to give informed consent to participate
4	• Willing to receive a single dose of an FDA-approved vaccine (either the influnza virus, pneumococcal or meningococcal vaccine)
5	**Arm III, Group 11:** Prior diagnosis of dengue infection or dengue fever.
6	**Arm III, Group 12:** Prior diagnosis of dengue hemorrhagic fever
7	**Arm III, Group 13:** Prior diagnosis of chikungunya virus infection.
8	**Arm III, Group 14:** Prior diagnosis of zika virus infection.

13.11 Exclusion Criteria

Please list participant exclusion criteria:

Order Number	Criteria
1	History of seizure disorder for Flumist group participants only.
1	For Flumist participants: Current illness that limits delivery to nasal airway (mild illness, such as diarrhea or mild respiratory infection with or without fever, and local infections do not apply)
1	For Flumist participants: Close contact with person with severely compromised immune system requiring isolation
2	• Egg allergy for influenza vaccine groups
3	• Prior allergic reaction to commercial vaccination
4	• In the opinion of the investigator, the volunteer is unlikely to comply with the study protocol.
5	• Is pregnant or lactating
6	• If Guillain-Barre syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the influenza vaccination will not be administered
7	• Poor venous access
8	• Participation in another clinical study of an investigational product currently or within the past 90 days, or expected participation during this study.
9	• Any clinically significant abnormality on medical history or physical examination that, in the opinion of the investigator, would preclude participation.
10	• Received any vaccine within the last 4 weeks
11	• Unable to complete study

14.0 Schedule of Events/Study Plan

14.1 Instructions:<u>New Studies:</u>

- ***The <u>iRIS Study Plan</u> has been phased out for new protocols.***
- ***A <u>Schedule of Events</u> (below) is required for all new studies involving interactions with human subjects.***
- ***<u>A template Schedule of Events</u> is available on the IRB website. For any new study, populate the template with the visits and procedures for the study.***
- ***The content of the Schedule of Events should be consistent with any descriptions of study procedures that may be in the protocol text and informed consent.***

- ***Attach the completed Schedule of Events to the protocol below.***

Existing Studies:
For existing studies, investigators may elect to update the existing Study Plan or may replace the Study Plan with a Schedule of Events, following the instructions above for new studies.

Attach Schedule of Events:

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
1.0	study_plan_	Schedule of Events				41.27 KB

Attach the Study Plan (an option only for studies with pre-existing Study Plans):

Select a template: Template 8 Select an arm: Screening

Procedure/Task Name	CPT Code	Screen Visit
Clinical Procedures		
Adverse Event Assessment		
Adverse Event /Serious Adverse Event Assessment		
Assessments (Nursing)		
Concomitant Medications		1
Height		1
Local/Systemic Reactogenicity Assessment		
Pre- and Post Procedure Vital Signs		
Vital Signs		1
Weight		1
Immunization / Vaccine		
Immunization - Group 10		
Immunization - Group 5 and 6		
Immunization - Group 7		
Immunization - Group 8 and 9		
Informed Consent Process		
Assess subject's knowledge and understanding of protocol		1
Assess subject's ongoing consent for participation		
HIV Consent		1
Informed Consent , Obtain Initial		1
Informed Consent, Review for Current Date and Version		
Obtain HIPAA Consent		1

Lab-Specimens: Urine		
MSKCC-C - Urinalysis with Microscopic	81001	1
POCT - Urine Pregnancy Test	81025	
Lab-Specimens: Venous Blood		
MSKCC-C - AST (Aspartate Aminotransferase)		1
MSKCC-C - Alanine Aminotransferase (ALT), Serum		1
MSKCC-C - BUN, Serum		1
MSKCC-C - Bilirubin, Conjugated, Serum		1
MSKCC-C - Bilirubin, Total, Serum		1
MSKCC-C - CBC w/Auto Differential		1
MSKCC-C - Calcium, Serum		1
MSKCC-C - Creatinine, Serum		1
MSKCC-C - Electrolytes, Serum		1
MSKCC-C - Glucose, Serum		1
MSKCC-C - Hepatitis B Surface Antigen, Serum		1
MSKCC-C - Hepatitis C Antibody		1
MSKCC-C - hCG, Qualitative, Serum		1
Research Blood - 3 10ml Green top tubes	36415	
Research Blood - 1 3.5ml SST top tube	36415	
Research Blood - 1 8.5ml SST top tube	36415	
Research Blood - 1.5 10ml Green top Tubes	36415	
Research Blood - 12 10ml Green top tubes	36415	
Research Blood - 2 8.5ml SST top tubes	36415	
Research Blood - 5 8.5ml SST top tubes	36415	
Research Blood - Pax Gene RNA tube	36415	
Lab-Specimens: other		
POCT Rapid HIV	86701-3	1
Medical History		
Interim history		
Medical History		1
Physical Examination		

Physical Examination		1
Targeted physical examination		
Procedures (Nursing)		
Venipuncture	36415	1
Subject Teaching		
Pregnancy Avoidance Counseling		1
CRF Forms		
Administrative Procedures		

*** What is the total number of outpatient visits for all participants projected for the next year?**

75

*** What is the average length of each outpatient visit (in hours)?**

1

*** What is the total number of Day Patient visits for all participants projected for the next year?**

0

*** What is the average length of each Day Patient visit (in hours)?**

0

*** What is the total number of inpatient days for all participants projected for the next year?**

0

15.0 Investigational and Support Medications

15.1 List all the investigational medications

See Help for link to Rockefeller University Research Pharmacy web page for additional information.

View Details	Drug Name	FDA Approved	IND Number
⊟	**Trade Drug Name:** FluMist Vaccine **Generic Drug Name:** **Investigational Drug Name:**	Yes	

Trade Drug Name:	FluMist Vaccine
Generic Drug Name:	
Investigational Drug Name:	

Identify the name of the manufacturer or source of investigational drug/biologic:	
Is the Drug FDA Approved:	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	
Frequency:	

Trade Drug Name: Menveo

⊟ **Generic Drug Name:** meningococcal conjugate vaccine Yes

Investigational Drug Name:

Trade Drug Name:	Menveo
Generic Drug Name:	meningococcal conjugate vaccine
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	
Is the Drug FDA Approved:	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	
Frequency:	

Trade Drug Name: Menomune

⊟ **Generic Drug Name:** Meningococcal Vaccine Yes

Investigational Drug Name:

Trade Drug Name:	Menomune
Generic Drug Name:	Meningococcal Vaccine
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	
Is the Drug FDA Approved:	Yes
Is an IND necessary	No
IND Number	

Who holds the IND:	N/A
IND details:	
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	
Frequency:	

Trade Drug Name: Fluzone ID

⊟ **Generic Drug Name:** Influenza Virus Vaccine Yes

Investigational Drug Name:

Trade Drug Name:	Fluzone ID
Generic Drug Name:	Influenza Virus Vaccine
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	
Is the Drug FDA Approved:	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	
Frequency:	

Trade Drug Name: Fluzone IM

⊟ **Generic Drug Name:** Influenza Virus Vaccine Yes

Investigational Drug Name:

Trade Drug Name:	Fluzone IM
Generic Drug Name:	Influenza Virus Vaccine
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	
Is the Drug FDA Approved:	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	

Frequency:	

Trade Drug Name: Pneumovax 23

⊟ **Generic Drug Name:** Pneumococcal Vaccine — Yes

Investigational Drug Name:

Trade Drug Name:	Pneumovax 23
Generic Drug Name:	Pneumococcal Vaccine
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	
Is the Drug FDA Approved:	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	
Frequency:	

Trade Drug Name: Prevnar

⊟ **Generic Drug Name:** Pneumococcal Vaccine — Yes

Investigational Drug Name:

Trade Drug Name:	Prevnar
Generic Drug Name:	Pneumococcal Vaccine
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	
Is the Drug FDA Approved:	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	
Frequency:	

15.2 * Will the study involve the use of a placebo?

○ Yes ◉ No

15.3 Study support medications are medications that will support the conduct of the study. Please list all support medications to be used in the study (include all prescription drugs, over the counter drugs herbs, and supplements).

16.0 Consent Procedure

16.1 * This study will use the following types of informed consent:

- [x] Informed Consent Form Standard - a standard consent form with instructions for adapting it to your study
- [ ] Consent Form Genetic- a consent form designed for a study where genetic testing (as defined by NYS law) is to be done in the CURRENT study
- [ ] Consent for studies including genome wide sequencing
- [ ] Pediatric Assent Form (To be used in addition to Consent) for Pediatric patients
- [x] Other (e.g., waivers, electronic informed consent)

Links to the **Standard Consent, Genetic Testing Consent** and the **Pediatric Assent** forms can be found in the Help link to the right, or these forms can be downloaded later on in the submission process.

16.2 * Indicate the consent process to be used. (See Help for CCTS SOP)

Describe how the required information is being presented to participants (consent form, orally, information sheet, etc.). Attach a copy of what is being presented to participants (usually the ICF and Assent forms).

Prior to the initiation of any study related procedures, the potential subjects will be given a copy of the most recent IRB stamped and approved informed consent to read. Additionally, the PI or study staff member who has been designated to consent will discuss the specifics of the study including but not limited to the purpose of the research, procedures, time commitment, required tasks, test article or device, alternative treatments, benefits, risks, confidentiality etc. in a comprehensible (non-scientific) manner, using language readily understandable by the subject. Subjects will be told that participation is voluntary and that, if they do not consent, they will not be penalized. The person consenting will assure the voluntariness of the subject.

Describe the circumstances under which consent will be obtained, where the process will take place and any waiting period between informing the prospective participant and obtaining consent.

A private, confidential setting will be provided for the potential subject to read and discuss the informed consent free from coercion, undue influence or constraints of time. All subjects will be given a chance to ask questions and express concerns. They will be given the option to take the consent home and discuss it with family, friends, and /or health care providers. After a subject and the person conducting the consenting signs and dates the consent, the subject will be given a copy of the signed informed consent form.
An enrollment note will be written in the source document as to who obtained consent, how, when, were questions asked and answered, and that a copy of the informed consent was given to the subject.

Describe the experience of the investigators designated for this task in the DOA in obtaining consent from participants.

Marina Caskey, MD, has extensive experience consenting human subjects for participation in research studies.

Joseph Colagreco DNP, NP-BC, and Taia Wang, MD, PhD, have demonstrated competency in consenting subjects for participation in research studies. This competency is based on attending a consenting class which includes regulations, the do's and don'ts and didactic role playing. It also includes observing the consenting process as performed by an experienced consenter and then consenting a subject to participate in a research study while being observed by the experienced consenter

.

How will it be determined that the participants or the participants' authorized representatives understand the information presented?

The "Teach Back" method will be used in the clinical research setting to ask research participants to repeat or “teach back” the information, concepts and directions that the staff member has attempted to convey to the subject. This method is used to assess comprehension and retention of protocol requirements, adverse event information, risks and benefits, and the subject's rights described in the Informed Consent process.

If English is not the participants' native language, how will written and/or verbal translation be provided?

Spanish-speaking volunteers may be enrolled in the study. For these potential volunteers, a certified Spanish translation of the IRB-approved informed consent form (ICF) will be used. For unexpected or isolated volunteers who are candidates for this study, who are native speakers of other languages, a telephonic interpreting service (such as Pacific Interpreters) will be used to facilitate the explanation of the study. The investigator will send the interpreter a copy of the study’s ICF in the language that needs to be interpreted. The consenting process will be conducted by reading the English ICF while the interpreter repeats the words in the language of choice. The interpreter will also translate questions and answers that occur during the informed consent discussion. At the end of the consenting process, if the participant agrees, he/she will sign the ICF in his/her native language in the presence of the investigator. The interpreter will sign the IRB-approved ICF as a witness, and will fax or email the signed copies to the investigator. The investigator will sign the IRB-approved ICF as the person conducting the consent discussion

Will any participants be cognitively impaired so that they may not have the capacity to give consent?

○ Yes ◉ No

For participants where it has been determined that they lack the capacity to give consent, describe the provisions for obtaining consent from the participants' legally authorized representative.

16.3 * Based on the demographics, will this study's participant population require foreign language consent form?

○ Yes ◉ No

16.4 * This study's consent procedure will require the following waivers: (See Help for additional information.)

◉ Waiver of one or more elements of informed consent, 45 CFR 46.116(f)
○ Waiver of documentation of informed consent, 45 CFR 46.117(c)
○ No waiver is requested

If a waiver is requested, please provide justification for the waiver here:

We are requesting a full waiver of informed consent for the use of the 150 restrospective samples because:
1) The use of the samples involves no more than minimal risk to the subjects;
2) The waiver will not adversely affect the rights and welfare of the subjects because the subjects consented to the future use of their samples in research;
3) The use of the samples in this research could not be practicably carried out because the RU research team will not be provided with identifiers, and thus will not have the ability to contact subjects

16.5 Will you obtain a Certificate of Confidentiality (CoC) for this study?

○ Yes ◉ No

16.6 * Does this study include video/audio recording, photography or other electronic recording of human participants?

○ Yes ◉ No

17.0 Recruitment and Advertising

For assistance consult CRSO to create a robust Recruitment Plan see Help.

17.1 * What is the plan for recruitment?

Overview: The CRROSS will recruit and prescreen 278 volunteers to achieve the enrollment goal of up to 215 volunteers for vaccination. As of the April 2016 amendment, the cohort will include an additional arm containing 100 participants in 4 groups: 25 participants with a history of dengue virus satisfying specific laboratory criteria, 25 additional participants with a history of dengue fever or dengue hemorrhagic fever and specific laboratory findings, 25 volunteers with a history of infection with chikungunya, and 25 volunteers with a history of infection with Zika virus.

Text below is provided for the Submission Recruitment Plan:
Feasibility and Assessment:
Incentives: 1) Altruism; 2) Compensation for efforts; 3) Opportunity to receive free FDA-approved flu vaccine
Challenges: 1) Must be able to provide documentation of the disease; 2) Participants must be willing to return for 4 visits within 3 weeks; 3) Potential language barrier with immigrant participants who are among the target populations

Issues relevant to rapid accrual: Positive: 1) Repository query yielded two potential volunteers with a history of dengue virus infection (recruited to LBE-0910); they may be helpful stakeholders; 2) Zika, and other tropical viral infections are currently very visible in the media raising awareness and a certain cache; 2) Negative: It may be necessary to form partnerships with healthcare providers serving the target populations to gain access to affected patients – effective partnerships take time to form, and the alignment of incentives to collaborate can be challenging, especially with a short timeline.

Projected enrollment timeline: The investigator plans to see participants up to 5 days/week which translates to screen/enrolling 1-10 volunteers a week. Assuming 1-2 weeks start up time, a few lost weeks for vacation, amendments, or other logistics, the target for complete accrual is 12 months. The CRSO will refer any participants prescreened through our services for further scheduling by the investigator.

Recruitment Implementation:
Advertising- CRROSS will place ads both in broadly distributed NY area newspapers (i.e Metro) as well as specific papers/platforms that are circulated among the target populations, namely individuals who have lived in or travel to areas with high rates of infection (i.e Caribbean Life, Caribbean American Weekly). The populations include individuals from the Dominican Republic, Puerto Rico, other Caribbean islands, and Brazil. Demographic data from ad vendors, and demographic mapping resources, such as **http://www.nytimes.com/interactive/2011/01/23/nyregion/20110123-nyc-ethnic-neighborhoods-map.html?_r=1&** are used to target advertising efforts when possible. Other media outlets will include internet (Voices of NY, Craigslist, Clinicaltrials.gov, **centerwatch.com**), radio (i.e WBLS 107.5 FM), and others as appropriately identified. **Research Volunteer Repository** Database – The investigator has agreed to associate protocol TWA-0804 with RKO-0648, the Research Volunteer Repository Protocol, enabling the CRROSS to query the existing volunteer database to identify a list of potential volunteers who have agreed to be contacted for future studies and who meet basic eligibility criteria. The CRROSS will contact potential volunteer as allowed to determine interest and will refer eligible and interested volunteers to the study coordinator/investigator. In parallel, the research team will seek and document the granting or denial of permission to contact volunteers about future studies.
Centralized Call Management – CRROSS will work with the research team to develop a protocol-specific pre-screening script based on IRB approved protocol eligibility criteria to prescreen volunteers who call 1800RUCARES. Potentially eligible candidates will be scheduled for the study team for further screening. CRROSS staff will also call volunteers based on Repository queries described above. Research teams are responsible to provide timely updates on pre/screening outcomes (through iRIS, etc.) to keep CRSO strategies on target.

Patient referral from Elmhurst Hospital, Queens, NY:
Doctors from Elmhurst Hospital, Joseph Masci and Maurice Policar, will refer interested individuals who have appropriate medical histories for Arm III to CRROSS for pre-screening.

17.2 *From the date of final IRB approval, how long will it take to complete enrollment of the study?

- ○ 6 Months
- ○ 12 Months
- ○ 18 Months
- ○ 24 Months
- ◉ More than 2 years (specify in years)

10 years

17.3 This Study

- ◉ Involves an intervention or comparison and a defined enrollment target
- ○ Is a natural history study with expected annual enrollment over many years
- ○ Is an exploratory mechanistic study
- ○ Other

17.4 This Study will enroll:

- ◉ Healthy volunteers
- ○ Individuals affected with a specific disease/disorder
- ○ Both

17.5 * Do you plan on using the Research Participant Repository (RKO-0648) ?

◉ Yes ○ No

17.6 * Are you screening or recruiting from or through a record review of an existing patient database of a healthcare provider?

○ Yes ◉ No

17.7 * Please describe how the Recruitment Plan addresses recruitment of the volunteers consistent with the demographics of the condition under study:

Recruitment is intended to yield volunteers from a variety of ethnic and socioeconomic backgrounds from the age range specified

17.8 * Do you plan to advertise directly to potential volunteers? (As opposed to relying on practitioner referrals or flyers to practitioners)

◉ Yes ○ No

17.9 * Do you plan to use the free, web-based volunteer registry, ResearchMatch.org, as a recruitment tool?

◉ Yes ○ No

18.0 Research Participant Repository (RKO-0648)

18.1 This protocol, will be linked with the Research Volunteer Screening/Recruitment Data Repository run by the Recruitment staff and the Clinical Research Support Office (protocol RKO-0648-1008). In order to participate in the generation of the Repository the PI will enter into a Collector/Collaborator agreement regarding the Repository. The role of Collector/Collaborator is to contribute to the Repository the name, contact and demographic information, recruitment referral information, and screening outcome information, as well as appropriate protocol specific screening information, of volunteers who are screened by telephone or in person for entry into the protocol regardless of the screening outcome. In addition to screening volunteers for the PI's current study, verbal consent will be obtained from the volunteers regarding their willingness to be contacted in the future about possible additional research studies. This permission may be obtained by the Recruitment office staff through the central Call Center. If the PI receives calls directly from participants for initial prescreening, then the PI is responsible for collecting the required information and conveying it to the Recruitment staff for data entry. The consent or withholding of permission will be recorded in the Repository as will the name of the person who obtained the permission. A volunteer's permission or declination will not affect their eligibility for my current protocol, or future protocols. The Recruitment staff of the Clinical Research Support Office may gather the Repository information and request the verbal consent of the volunteer for re-contacting on my behalf as part of our recruitment plan. In order to benefit from the Repository, the PI will enter into a Recipient/Collaborator agreement with the Repository. The Recipient/Collaborator may receive from the Repository pre-screened lists of potentially eligible participants for his/her study as a means to facilitate recruitment. The Recruitment staff will prepare the Repository queries according to the protocol eligibility requirements and available Repository information, and may re-affirm permission to re-contact volunteers as necessary. The PI may use the information and names in the list from the Repository only for the current study and may not save the list to use for a future study of his/her own, nor may he/she share the list with colleagues for other studies."

19.0 Utilization of ResearchMatch.org

19.1 Utilization of ResearchMatch.org for Recruitment

Basic information regarding this tool:

- **ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University. There is no cost for researchers at participating institutions in the ResearchMatch.org Network to use ResearchMatch.org. The Vanderbilt IRB provides oversight for ResearchMatch.org as a recruitment tool and this has been documented within the ResearchMatch.org IRB Letter of Understanding which was executed by Dr. Gotschlich in October, 2009. However, individual requests to use ResearchMatch.org as a recruitment tool must be submitted to this institutions' IRB.**

Registration:

- **This recruitment tool may be utilized once the PI or research staff registers for recruitment access through ResearchMatch.org and the Institutional Liaison provides approval.**
- **The ResearchMatch.org Institutional Liaison will review the study information and evidence of IRB approval. He/she will set the researcher's expiration date to mirror that of the study's IRB approval.**

Search Capability:

- **After being granted recruitment access, the researcher can search for appropriate matches amongst the non-identifiable ResearchMatch.org Volunteer profiles in the system. He/she can enter study inclusion/exclusion criteria in the ResearchMatch.org Search Builder which will yield a list of potential matches to the study's criteria.**

Contacting ResearchMatch.org Volunteers:

- **Once yielding a list of potential matches (ResearchMatch.org Volunteers), the researcher will send out IRB-approved content that will be the initial recruitment message that these volunteers receive about the study through ResearchMatch.org. The study's recruitment message will be inserted into the standard ResearchMatch.org electronic notification that informs possible matched Volunteers that he/she has been identified as a potential match for the study. The secure ResearchMatch.org clearinghouse will route this standard ResearchMatch.org email notification. These potential matching volunteers will have the option of replying yes, no, or not respond through a set of quick links available in this notification to the study announcement. THE CONTACT MESSAGE WILL NOT INCLUDE THE STUDY'S DIRECT CONTACT INFORMATION (e.g. EMAIL, PHONE). By responding yes, the Volunteer has authorized ResearchMatch.org to release his/her contact information to the researcher. The researcher will be responsible for managing this contact information as called for by this IRB-approved study protocol.**

Study Management in ResearchMatch.org:

- **Researchers (and the Liaison) can view information regarding his/her study's status in ResearchMatch.org (e.g. number of volunteers contacted for the study via ResearchMatch.org to date, response rate of volunteers, etc.). ResearchMatch.org will also be collecting aggregate data regarding the status of ResearchMatch.org volunteers within the study. Volunteers consent to this within the ResearchMatch.org Volunteer Agreement. This information will allow the researcher to indicate where the Volunteer currently stands within the recruitment process and thus will help the researcher monitor the utility and effectiveness of using this resource (e.g. Did not contact, Not eligible, Enrolled, Completed, etc.).**

20.0 Potential Benefits to Participants

20.1 * Will participation in this study provide direct benefits to the participant?

(•) Yes ( ) No

20.2 If Yes, describe the potential direct benefits:

Volunteers will receive without cost an FDA-approved vaccine.

21.0 Potential Risks to Participants

21.1 * Describe any potential risks: physical, psychological, social, legal or other and assess their likelihood and seriousness. Indicate risks both to the participants and to the embryo or fetus if the participant is or may become pregnant. Please provide the potential risks below:

Blood draw:the risks associated with a blood draw are generally minor. They are mild pain at the needle site (common), local bruising at needle site (rare), infection and fainting (extremely rare).

Influenza Vaccine (IM administration):
· Most common (≥10%) injection-site reactions were injection site tenderness, pain, swelling and arm stiffness.
· Most common (≥10%) systemic adverse events were headache and myalgia.
· Life-threatening allergic reactions from vaccines are very rare. If they do occur, it is usually within a few minutes to a few hours after the shot.
· In 1976, a type of inactivated influenza (swine flu) vaccine was associated with Guillain-Barré Syndrome (GBS). Since then, flu vaccines have not been clearly linked to GBS. However, if there is a risk of GBS from current flu vaccines, it would be no more than 1 or 2 cases per million people vaccinated. This is much lower than the risk of severe influenza, which can be prevented by vaccination.

Influenza Vaccine (ID administration):
· The most common injection-site reactions were erythema (>75%) induration (>50%), swelling (>50%), pain (>50%), and pruritus (>40%). Erythema, induration, swelling and pruritus occurred more frequently following intradermal administration.
· The most common solicited systemic adverse events were headache, myalgia, and malaise (>20%).

Flumist Vaccine (Intranasal administration):
· The most common solicited adverse reactions were runny nose or nasal congestion (44%) and sore throat (19%).

Meningococcal Vaccine (Menveo):
· In clinical trials, the most frequently occurring adverse events (≥10%) in subjects 11 to 55 years of age who received Menveo were pain at the injection site, headache, myalgia, malaise, and nausea.
· You should not receive Menveo if you have had a severe allergic reaction to any ingredient of the vaccine, or if you have had a severe allergic reaction to a vaccine containing similar components as Menveo.
· Following vaccination with another US-licensed meningococcal conjugate vaccine, an evaluation of postmarketing adverse events suggested a potential for increased risk of Guillain-Barré Syndrome (GBS). There is not enough information to evaluate if a risk of GBS exists following administration of Menveo.

· Serious allergic reactions, within a few minutes to a few hours of the shot, are very rare.

Meningococcal Vaccine (Menomune):
· Common (>10%) adverse events in persons 11 to 55 years of age were pain, redness, and induration at the injection site, headache, fatigue, malaise, arthralgia, and diarrhea.
· Serious allergic reactions, within a few minutes to a few hours of the shot, are very rare.

Pneumovax Vaccine (Pneumovax 23)
· The most common adverse reactions, reported in >10% of subjects were: injection-site pain/soreness/tenderness (60.0%), injection-site swelling/induration (20.3%), headache (17.6%), injection-site erythema (16.4%), asthenia and fatigue (13.2%), and myalgia (11.9%).

Pneumovax Vaccine (Prevnar):
· In adults aged 50 years and older the commonly reported solicited adverse reactions were pain at the injection site (>50%), fatigue (>30%), headache (>20%), muscle pain (>20%), joint pain (>10%), decreased appetite (>10%), injection site redness (>10%), injection site swelling (>10%), limitation of arm movement (>10%), chills (>5%) or rash (>5%).

22.0 Procedures to Minimize Risks

22.1 * Describe the procedures for protecting against or minimizing any potential risks, and include an assessment of their likely effectiveness. Include a discussion of confidentiality safeguards, where relevant, and arrangements for providing medical treatment, if needed.

- Volunteers will be monitored for a minimum of 20 minutes after receiving their vaccination
- Volunteers will receive a telephone call or email from a member of the research staff 2 weeks (+/- 2 days) after receiving their vaccination to assess for side effects to the vaccination. If a volunteer complains of any moderate greater adverse event, they will be asked to return to the outpatient clinic for an evaluation
- All blood will be drawn by licensed professionals using sterile technique

23.0 Alternative Methods or Treatments

23.1 * Describe alternative methods or treatments for the disease(s) under study, if any, that were considered and why they will not be used:

A volunteer may choose not to participate in this study

24.0 Data and Safety Monitoring

This section describes the Data and Safety Monitoring Plan (DSMP) required of each protocol undertaken at the CCTS according to HRPP and NIH policies Notice 98 -084 and Notice 00-038, as cited in Help Sections below. Depending on the level or risk and trial phase, some protocols will need Data and Safety Monitoring Boards.

24.1 * Overall Risk Classification

An estimate of risk is necessary to evaluate the adequacy of the planned monitoring. The HELP section provides guidance in making the risk assessment.

Read the risk definitions and examples of risk in the HELP section and select the risk category that best describes the current study.

If your assessment differs from the definitions the HELP section, describe any factors that modify your judgment of the overall risk in the text box after the risk designation.

- ○ MINIMAL RISK
- ◉ LOW RISK
- ○ MODERATE RISK
- ○ SIGNIFICANT RISK

Please provide any optional description(s):

24.2 Protocols Involving Minors

The chance of direct benefit to the child, or to understanding a disorder not otherwise understood, may be major factors in justifying more than minimal risk in research involving children.

Based on the above definitions, please specify your study's risk classification below:

- ○ NOT GREATER THAN MINIMAL RISK (the risk of daily life to a healthy child living in a safe environment) 45 CFR 46.404
- ○ GREATER THAN MINIMAL RISK WITH DIRECT BENEFIT TO PARTICIPANT; 45 CFR 46.405
- ○ GREATER THAN MINIMAL RISK, NO DIRECT BENEFIT, BUT BENEFIT TO UNDERSTANDING OF PARTICPANT'S DISORDER; 45 CFR 46.406
- ○ RESEARCH NOT OTHERWISE APPROVED PRESENTING OPPORTUNITY TO UNDERSTAND, PREVENT OR ALLEVIATE SERIOUS PROBLEM AFFECTING CHILDREN 45 CFR 46.407 (cannot be approved by IRB; requires public comment)

24.3 DSMB

1. The NIH requires that all SIGNIFICANT RISK protocols have a **Data and Safety Monitoring Board** and provide information about the expertise and independence of that Board
2. Phase III trials require a Data and Safety Monitoring Board,
3. A DSMB may be appropriate for some Phase I and II protocols. (See Help for examples.)
4. It is the investigator's responsibility to report to the IRB, the findings and recommendations of the DSMB as they become available.

Please specify:

- ○ A DSMB is required for this study
- ◉ A DSMB is not required for this study
- ○ Unsure

If a DSMB is not required, but is being constituted for other reasons, please explain:

24.4 * Safety Review

Select one:

- ◉ Safety Review is conducted as follows: Laboratory results for research volunteers will be reviewed in a timely manner, usually within 24 hours of receipt by a licensed practitioner. The potential clinical significance of any abnormal finding will be documented in the medical and research record(s), and an appropriate plan or referral developed. The PI's review of safety issues at research team rounds will be documented in the meeting minutes.

○ Protocol Specific

24.5 Monitoring

Monitoring Personnel: See Help Bubble to the right.

Internal Monitoring

The PI or his/her designee shall conduct internal monitoring to assure the safe and proper conduct of the protocol and all the elements list above in monitoring, following the general principles of quality management. The intensity and frequency of internal monitoring will depend on the protocol risk to participants, the experience of the PI and research team, rate of enrollment, and specific details of the protocol.

Internal monitoring of informed consent and eligibility documentation will be conducted by the research team shortly after enrollment begins. Internal monitoring activities will be documented by logs, meeting minutes or other systematic means.

Specify the research team members who will conduct the internal monitoring of the study (see Help for who may monitor):

All members of the study team (Taia Wang, MD, PhD, Marina Caskey, MD, and Joseph Colagreco, DNP, NP-BC) will meet regularly to discuss any protocol, volunteer, recruitment and regulatory issues.

For new investigators: Internal monitoring should be conducted at least monthly by new investigators until there are essentially no findings to correct at each review.

External Monitoring

* Is external monitoring planned for this protocol?

○ Yes
◉ No
○ Unsure

If external monitoring is planned, please specify (see Help for who may monitor):

○ (Significant Risk) External monitoring will occur at least every six weeks unless there is no enrollment
○ (Moderate Risk) External monitoring will occur at least quarterly
○ (Low or Minimal Risk) External monitoring will occur at least annually

If external monitoring is planned, please specify the name of the monitor:

☐ Note that copies of external monitoring reports must be supplied to the IRB and the CRSO as soon as they are made available

Additionally, audits of the research records of minimal, moderate or significant-risk protocols may be performed by the CRSO staff on a random basis or as part of a prospectively identified auditing plan.

24.6 Adverse Event Classification

Adverse events are classified by definition, severity, and association with the investigational trial.

Definition of an Adverse Event
Any unfavorable or unintended sign (including abnormal lab findings), symptom or disease temporally associated with the use of a medical treatment or procedure, or protocol, regardless of whether it is considered related to the medical treatment or procedure or protocol.

Definition of a Serious Adverse Event
Any unanticipated event that involves the following:

o results in death
o is life-threatening
o requires hospitalization or prolongs existing hospitalization
o results in persistent or significant disability/incapacity
o is any medical event which requires treatment to prevent one of the outcomes listed above
Other events can be classified as "serious adverse events" at the discretion of the PI.

Definition of Anticipated/Expected Adverse Event

Any adverse event, which has been reported in the Investigator's Brochure, package insert, safety reports, clinical protocol, consent form or listed in the NCI agent-specific Expected Adverse Event List[3], is classified as an expected adverse event. The investigator must provide the available data of known adverse events and toxicities that have been associated with the study drug, device, intervention, or procedures. This information helps to define the level of risk of the trial and enables safety monitoring. A minimal risk trial may not have any defined risks and a statement to that effect is sufficient to meet the DSMP requirements.

Definition of an Unanticipated/Unexpected Adverse Event
Any adverse event that is not consistent with the known, predicted possible effects of the research protocol. An unexpected adverse event varies in nature, intensity or frequency from information on the investigational product provided in the Investigator's Brochure, package insert, safety reports, clinical protocol, or listed in the consent form.

Definition of an Unanticipated Problem (UaP)
A UaP is an event or circumstance that meets all the following three criteria: [1] the nature, severity, frequency of the event(s) or information was not expected in the descriptions in the study documents or the characteristics of the participant population being studied; [2] there is a reasonable possibility that the procedures involved in the research caused or are linked in a significant way to the problem; [3]the event or information suggests that the research places particpants or others at a greater risk of harm than was previously known or recognized (including physical, psychological, economic, or social harm.

Grade and Relatedness of Adverse Events:

Adverse Events are graded for severity and scored for relatedness to the protocol, according to a published scale. Several standardized AE Reporting scales are available. (See Help for links to these scales.)

* Please indicate the scale you intend to use:

- ○ CTC v2.0 (http://ctep.info.nih.gov/reporting/ctc.html)
- ○ CTCAE v3.0 (http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf)
- ◉ CTCAE v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)
- ○ CTCAE v5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf)
- ○ AIDS Clinical Trials Group (http://aactg.s-3.com/)
- ○ Other

24.7 Reporting Adverse Events

All AEs will be reported to the IRB at least annually.

Reporting Serious AEs

☑ Serious Adverse Events, (SAEs) will be reported to the IRB according to policy, within two working days of identification of the SAE.

Select all that apply:

☐ SAEs will be reported to the Sponsor and or ESCROW

SAEs will be reported to the sponsor within how many days of the event?

☐ SAEs will be reported directly to the FDA, per 21 CFR 312

SAEs must be reported directly to the FDA within 7 days of the event by the investigator/sponsor.

☐ SAEs will be reported to another entity

Describe:

Reporting Unanticipated AEs:

Select all that apply:

☑ UAEs will be reported to the IRB

UAEs that are related and greater than moderate severity must be reported to the IRB according to policy, within two working days of identification of the UAE.

☐ UAEs will be reported to the Sponsor

UAE will be reported to the sponsor within how many days of the event?

☐ UAEs will be reported to the FDA, per 21 CRF 312

UAEs will be reported to the FDA, per 21 CRF 312, within 15 days.

☐ UAEs will be reported to another entity

Describe:

24.8 Reporting Unanticipated Problems

☑ Unanticipated problems involving risks to participants or others will be reported to the IRB and the CRSO within five working days.

24.9 CLIA/CLEP

Only laboratory and research tests that are CLIA/CLEP certified or waived may be used to determine eligibility, shared with research volunteers, and used in clinical decision making.

Select if applicable:

☑ This study includes tests that are not CLIA/CLEP certified; the results of such tests will not be used in clinical decision making, or to determine eligibility, or shared with participants or their health care providers.

24.10 Tissue Repository

Human Tissue and Data Repositories collect, store, and distribute human tissue materials and or data for research purposes. Repository activities involve three components: (i) the

collectors of tissue samples\data; (ii) the repository storage and data management center; and (iii) the recipient investigators.

* Select one:

- (•) I DO NOT intend to collect, store, and distribute human tissue materials for research purposes
- ( ) I DO intend to collect, store, and distribute human tissue materials for research purposes, therefore this protocol entails the Operation of a Tissue Repository. The IRB requires that the protocol specify the conditions under which data and specimens may be accepted and shared, and ensuring adequate provisions to protect the privacy of participants and maintain the confidentiality of data.

If you do intend to collect, store, and distribute human tissue materials, you will be asked to upload the following documents later on in the submission:

- A Sample collection protocol (for tissue collector collaborators to follow) and informed consent document for distribution to tissue collectors and their local IRBs.
- A Certificate of Confidentiality (to protect confidentiality of repository specimens and data).
- A Recipients Agreement describing the commitment of the recipient to preserve the anonymity of the samples shared.

25.0 Toxicity Management and Stopping Rules

25.1 * Describe any drug toxicity or other conditions under which the participation of a participant or the conduct of the study would be stopped in order to maximize safety (e.g., toxicity management and stopping rules):

Not applicable.

*** Indicate withdrawal criteria and procedures below:**

Volunteers may be involuntarily withdrawn from the study if:
- They fail to keep appointments.
- Termination or cancellation of the research study by the investigator or the Rockefeller University Institutional Review Board.
- There is a significant adverse event to the participant or to others in the study,

26.0 Compensation/Costs

26.1 *Will any compensation be offered to participants in return for their participation, e.g., direct payment, medical care, tests, etc.?

- ( ) No
- (•) Yes (Please describe)

Please Describe

Volunteers will be compensated $75 for their vaccine visit, $35 for the follow-up blood draw visits except for the final visit at week 12, for which participants will be compensated $75. Participants who return for the 6-12 month visit will be compensated $50.

It is expected that volunteers for Arm 3 will be more likely to live outside of the immediate area, as patients with prior flavivirus or alphavirus infection are relatively rare. In consideration of anticipated travel time for volunteers in Arm 3, participants will receive $25 for the screening visit, and

compensation will be a minimum of $100 for each visit.

26.2 * Will there be any costs to participants associated with their participation in research?

○ Yes ◉ No

27.0 Bibliography

27.1 Enter your bibliography below:

References:

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28.0 Appendices

28.1 Enter your appendices below:

None

29.0 Funding

29.1 * Do you have sufficient financial resources to support your study?

(•) Yes ( ) No

29.2 If this study is/was pilot funded, please specify dates of funding:

From date:

12/04/2015

To date:

06/30/2016

29.3 Source of investigational agents:

( ) N/A (no investigational agents)
( ) Provided by a pharmaceutical sponsor/partner with funding as described below
( ) Provided by a pharmaceutical sponsor/partner without additional funding
( ) Provided by investigator, participants, or other

29.4 Specify funding by Rockefeller University, industry sponsor and/or grant:

Search for a sponsor

	Sponsor	Funding
Rockefeller University	Ravetch Laboratory	☑
Industry		
Grant	NIH/NIAID	☑

Pilot Award			

29.5 List grants in which this study is named:

PHS or Non-PHS	Program	Grant Number	Grant Name	From Date	To Date
PHS	NIH/NIAID	1U19AI111825-01	Integrating innate and adaptive pathways in vaccine responses	04/01/2019	03/31/2024
PHS	NIH/NIAID	U19AI109946-01	Mechanisms of broadly neutralizing humoral immunity against influenza viruses	05/01/2014	04/30/2019

30.0 Clinical Services

30.1 *What is the general health status of your study group(s)?

- [x] Well/Minimally Ill
- [ ] Moderately Ill
- [ ] Severely Ill
- [ ] Other
- [ ] Not Applicable

If other than Well/Minimally Ill, please describe:

30.2 * Does your study group have special care needs?

○ Yes ◉ No

30.3 * Does your study have special equipment needs?

○ Yes ◉ No

30.4 * Will you require storage space on the clinical units for supplies to conduct this study?

○ Yes ◉ No

30.5 * Is special training of hospital staff required?

○ Yes ◉ No

31.0 Pharmacy Services

31.1 * **Does the study require Pharmacy Services?**

(•) Yes ( ) No

If Yes, please proceed to next section.

31.2 Types of pharmacy services required:

- [x] Dispensing
- [x] Randomization
- [ ] Compounding
- [ ] Other

31.3 Dispensing:

- [ ] Sponsor supplied drugs
- [ ] Pharmacy supplied drugs
- [ ] Other

31.4 Type of medication(s):

- [x] Injectable
- [ ] Ophthalmic
- [ ] Inhalational
- [ ] Topical
- [ ] Suppository
- [ ] Other

If Injectable, please specify:

- [x] Monday-Friday 8:30AM-5PM
- [ ] Off-hours [all other days/times]

32.0 Bionutrition

32.1 * **Will study require patient meals?**

( ) Yes (•) No

If Yes, please specify:

Type of Diet	In/Outpatient	Pack Meal
Standard	☐ Inpatient ☐ Outpatient	( ) Pack Meal
Therapeutic	☐ Inpatient ☐ Outpatient	( ) Pack Meal

Research Diet	☐ Inpatient ☐ Outpatient	○ Pack Meal
Formula Diet	☐ Inpatient ☐ Outpatient	○ Pack Meal

Nutrient(s) to be controlled (specify):

32.2 Will meal times be altered?

○ Yes ○ No

If Yes, please explain:

32.3 Does the protocol require any of the following activities?

☐ Food Frequency Questionnaire
☐ Bod Pod/ Anthropometric Measurements
☐ Diet History/ Food Records
☐ Diet/ Nutrition Education

32.4 Will food be provided to caregiver, parent or significant other?

○ Yes ○ No

32.5 For metabolic diets, is diet homogenization required for nutrient analysis by independent lab?

○ Yes
○ No
○ N/A

33.0 Clinical and Translational Research Facilitation Office

33.1 Indicate navigation assistance requested and/or received in the development of the study:

	Requested	Received
Protocol Development	☑	☑
Protocol Implementation	☑	☑
Protocol Conduct	☑	☑
ACCTS/IRB Submission	☑	☑

33.2 Indicate additional education assistance requested and/or received in the development of the study:

	Requested	Received
IND	☐	☐
IDE	☐	☐
Team Science Education	☐	☐
Study Progress Meeting	☐	☐
Investigator Responsibilities	☐	☐
Regulatory Binder/Folder	☑	☑
Source Documentation	☑	☑
Participant Involvement in Research	☐	☐

34.0 Clinical Research Support Office Resources (CRSO)

34.1 Indicate regulatory input assistance requested and/or received in the development of the study:

Regulatory Support/Design	Requested	Received
General, Vulnerable Populations, Minors, Group Harms	☐	☐
IND/IDE advice, assistance, and referral	☐	☐
Informed Consent/Assent	☐	☐
Data Safety Monitoring Plan	☐	☐

Clinical Trial Registration	☐	☐
Plan For Return of Research Results	☐	☐
Audit/Monitoring Service, Referrals, SOPs	☐	☐

34.2 Indicate recruitment assistance requested and/or received in the development of the study:

Recruitment of Participants	Requested	Received
Recruitment Planning and/or written Plan	☑	☑
Advertising Strategy, Content, Placement	☑	☑
Repository/Research Match Queries	☑	☑
Call Center/Prescreening/Scheduling	☑	☑
Cost Sharing for Advertising	☐	☐

34.3 Indicate community engaging assistance requested and/or received in the development of the study:

Community Engagement	Requested	Received
PHI Statement/Engaging Stakeholders Section	☐	☐
CEnR Navigation – fostering pt/community partnership	☐	☐
Outreach to community/partner/advocacy group/CE Studio	☐	☐

34.4 Indicate other assistance requested and/or received in the development of the study:

Other	Requested	Received
Survey design, fielding, validation	☐	☐
Data transfer and security planning	☐	☐

35.0

BERD: Biostatistics, Epidemiology and Research Design Resource

35.1 Indicate the Biostatistical assistance requested and/or received in the development of this study:

	Requested	Received
Development of experimental design	☐	☐
Power analysis/Sample size determination (# of subjects)	☐	☐
Navigation (Did Statistician participate in a navigation meeting)	☐	☐
Randomization schedule	☐	☐
Data analysis	☐	☐
Development of new statistical techniques for data analysis (Statistical research)	☐	☐
Protocol implementation	☐	☐
Other	☐	☐

35.2 If you are/will be using data analysis specify:

- [ ] Exploratory
- [ ] Descriptive
- [ ] Hypothesis testing
- [ ] Statistical modeling
- [ ] Other

35.3 If you are/will be assisted with protocol implementation, specify:

- [ ] Publication
- [ ] Conference
- [ ] Other (type of dissemination)
- [ ] Grant(s)

35.4 Please select the Biostatistician on this Protocol:

- [x] Roger Vaughan, DrPH
- [ ] Caroline Jiang, MS
- [ ] Sandra Garcet, PhD
- [ ] Adam Qureshi, MA
- [ ] Other

36.0 Biomedical Informatics Resources

36.1 Indicate Bioinformatics assistance requested and/or received in the development of this study:

	Requested	Received
Microarray analysis	☐	☐
Pathway analysis	☐	☐
RNA-seq analysis	☐	☐
Bioinformatics training and consultation	☐	☐
Bioinformatics experimental design	☐	☐
HPC computing	☐	☐
Other	☐	☐

36.2 If you are/will be using pathway analysis software, specify:

- ☐ Ingenuity IPA
- ☐ David
- ☐ GSEA
- ☐ Other

36.3 If you are/will be using RNAseq analysis software, specify:

- ☐ Tophat
- ☐ Cufflinks
- ☐ Cuffdiff
- ☐ CummRbund
- ☐ STAR
- ☐ featureCounts
- ☐ DESeq2
- ☐ VOOM
- ☐ RNA-SeQC

If other, specify:

36.4 Indicate Medical Informatics assistance requested and/or received in the development of this study:

	Requested	Received
Data storage inside of iRIS	☐	☐
Redcap Database	☐	☐
Custom or Ad Hoc reports	☐	☐
Study plan creation	☐	☐
Specialize database or custom software	☐	☐
Other	☐	☐

37.0 HIPAA Form

37.1 A study's specific HIPAA form signed by the volunteer is required for institutions that are HIPAA covered entities so that they may communicate Private Health Information (PHI) to the Investigator.

Below, Memorial Sloan Kettering Cancer Center, New York-Presbyterian Hospital and Weill Medical College of Cornell University are listed so that that they may report laboratory results and X-ray readings respectively. If you foresee that any other entity may need to provide PHI then add them to the field highlighted in green.

37.2 Name of Study:

An open label study of IgG Fc glycan composition in human immunity

37.3 Principal Investigator:

Taia Wang, MD, PhD

37.4 Industry Sponsor:

If the funding source is industry please type in the sponsor here

Who may obtain, use, and/or disclose your health information?

The following persons and organizations may obtain, use, or disclose health information about you.

- The Principal Investigator(s) listed at the top of this form, and persons who assist the Investigator(s) in carrying out the research
- Each research site for this study, including The Rockefeller University, and the research management and support staff and the medical staff at each site
- Health care providers who have provided in the past, or currently provide, health care services to you
- Laboratories and other persons and organizations that will analyze your health information and/or biological samples as part of this study, including Memorial Sloan Kettering Cancer Center, New York-Presbyterian Hospital and Weill Medical College of Cornell University

Other entities that may need to provide PHI:

- Members and staff of the Institutional Review Board and other boards and committees that watch over research at The Rockefeller University
- Members and staff of The Rockefeller University's Office of Sponsored Research
- The sponsor(s) of the research, named above, and persons who watch over the research for the sponsor(s)
- The United States Food and Drug Administration, other government agencies, regulatory entities and Rockefeller University consultants that watch over the safety, effectiveness, and quality of research and/or fund The Rockefeller University Hospital
- Others (as described here):

What information will be obtained, used, or disclosed?

The persons and organizations listed above may obtain, use, and disclose:

- Information about you that is created or collected during the research study (but not including any HIV-related information)
- Health information in your medical records that is relevant to the research study (but not including any HIV-related information)
- **And**, if checked below:

___ HIV-related information (this includes any information indicating that you have had an HIV-related test or have HIV infection, HIV-related illness, or AIDS, as well as information that could

indicate you may have been exposed to HIV)
___ Other information (as described here):

_____
_____
_____
_____

- Other information (as described here):

By signing this form, you give permission to the persons and organizations listed above to obtain, use and disclose your health information noted above.

How will your health information be used?

The health information noted above, as well as information shown by the boxes checked above (if any), may be obtained, used, and disclosed:

- to conduct the research study explained to you during the informed consent process; and
- to assure the quality, safety, and effectiveness of the research study

Please note that the persons and organizations listed above may re-use or further disclose your information if they are permitted by law to do so.

What are your rights?

It is your right to refuse to sign this authorization form. If you do not sign this form, you will not be able to participate in the research study. Your health care outside the study will not be affected. The payment for your health care and your health care benefits will not be affected.
If you sign this authorization form, you will have the right to withdraw it at any time except to the extent that the persons and organizations listed above:

- have already taken action based upon your authorization;
- need the previously collected information to complete analysis and reports of data for this research; or
- will continue to use and disclose previously collected information as permitted by the informed consent form signed by you (except as to HIV-related information, for which disclosure to new persons or organizations will not occur unless permitted by federal or state law).

If you withdraw the authorization, you will not be permitted to continue taking part in the research study. This authorization form will not expire unless you withdraw it. If you want to withdraw this authorization, please write to the above named investigators.
You have a right to see and copy your health information described in this authorization form in accordance with The Rockefeller University's policies; in certain circumstances where the integrity of the study will be affected, you will not be able to obtain your health records in this study until the study has been completed.
You will receive a copy of this form after you have signed it.

Notice Concerning HIV-Related Information

If you are authorizing the release of HIV-related information, you should be aware that such information may not be shared without your approval unless permitted by federal or state law. You also have a right to request a list of people who may receive or use your HIV-related information without authorization. If you experience discrimination because of the release or disclosure of HIV-related information, you may contact the New York State Division of Human Rights at (212) 480-2493 or the New York City Commission of Human Rights at (212) 306-7450. These agencies are responsible for protecting your rights.

Your signature

I have read this form, and all of my questions have been answered. By signing below, I acknowledge that I have read and accept all of the information above.

Signature of participant or participant's legal representative

Date

Printed name of participant

Printed name of legal representative (if applicable)

Representative's relationship to participant

THE STUDY PARTICIPANT OR HIS OR HER PERSONAL REPRESENTATIVE MUST BE PROVIDED WITH A COPY OF THIS FORM AFTER IT HAS BEEN SIGNED.

38.0 End of Application Form

38.1 The study application form is complete.

The next step in the submission process is to gather attachments before proceeding to the submission form.

The following submission reports are generated in the Lab/Dept Reports menu, Submission Reports section:

- **Delegation of Authority** (if applicable, and if not previously generated)
- **HIPAA form** (if applicable)
- **CCTS Utilization Report** (required for all submissions)
- **Study Progress Report** (if the study has been managed in iRIS for a minimum of one year, generate the Progress Report from the report menu in iRIS. if the study has not been managed in iRIS for one year, complete the Progress Report located on the IRB website.)

All other required forms can be downloaded from the corresponding sections' help links above or from the IRB website.