Cover sheet

Most recent IRB approved protocol

4-13-17

Title: ZOSTAVAX in Persons Imminently Receiving Chemotherapy for Solid Organ Tumors

NCT02444936

PI: David H. Canaday, MD
Cleveland VA

IRB #: 14044-H30
(Assigned by IRB Office)

CPA #: 7304
(Assigned by IRB Office)

Approved
4/13/17
Cleveland VAMC
Institutional Review Board

Form Directions: *Form is protected (user has limited access to the fill-in fields). Use the tab key or mouse to navigate the fill-in fields. Formatting is limited in the text fields (no bulleted lists, numbering, etc). In the event that the user is unable to navigate through the protected document or would like to format a document, the user can disable the "protected" feature (select "Review" then "Restrict Ending" then "Stop Protection"). Please do not delete or modify questions..*

Louis Stokes Cleveland Department of Veterans Affairs Medical Center Research Plan

Please contact the IRB office if you have any questions at (216) 791-3800 ext. 4658.

☐ **Request for Expedited IRB Review Form attached**

Human Subject Research: Human subject research means research involving interaction or intervention with living human beings or access to identifiable private information of living human beings.

Research Plan: The information requested in the Research Plan is designed to provide the IRB with the necessary information such that it can make the federally required determinations codified at 38 CFR Part 16, 21 CFR Parts 50, 54, & 56, and 45 CFR Part 46

The **Research Plan** is to be written so that the non-scientist/non-medical members of the IRB can understand the research proposed. Define all abbreviations and terms that are not part of common language.

Version Date: This should be updated subsequently with every modification to any part of the Research Plan. Any modification to this document, no matter how minor, must be reviewed and approved by the IRB prior to implementation. The Research Plan will be stamped with the date of IRB approval

Section 1 – General Information

1. **Version Date:** 3-23-17

2. **Title of Project:** Shingles vaccine in oncology patients

3. **Principal Investigator (PI)** *(name & degrees)*: David Canaday, MD

   E-mail: dxc44@case.edu

   Pager Number/Cell Phone Number: 216-368-8901 UH pager 35324

4. **Research Contact/Research Coordinator** *(name, degrees)*: **Richard Banks**

   E-mail: Richard.banks2@va.gov

   Pager Number/Cell Phone Number: ext 6032

Section 2 – Research Sites and Sponsor

5. Please list all Research Sites in addition to Louis Stokes Cleveland DVA Medical Center (LSCDVAMC); The Cleveland VA is our site. Dr. Ken Schmader at Duke University and the Durham VA will also be funded by Merck and run 30 subjects there. He will send us coded blood samples to analyze with our samples. His samples will come from the Duke University site not their VA.

International studies when the PI is the Lead Investigator list the countries:

a. When study procedures including analysis of identifiable samples or data involving LSCDVAMC enrolled subjects will be conducted at any site other than the LSCDVAMC please provide the following:

Name and contact information for the site:

Describe the plan for communicating protocol amendments, reports of serious adverse events, reports of unanticipated problems involving risks to subjects or others, interim reports, and DSMB reports to external sites.

*** When the LSCDVAMC is considered the coordinating center and the PI the lead investigator on cooperative research or a multi-center trial contact AO/Research Holly.Henry@va.gov.**

6. Sponsor or other Support *(list industry sponsor, government support, etc.)*:

Merck

Section 3 – Research Design and Procedures

7. Definitions- Provide a list of all abbreviations and specialized terms to be used in this document and their definitions:

Abbreviations / Specialized Terms *(Use the Enter key in this column to insert additional abbreviations and their definitions)*	**Definition**
LSCDVAMC	Louis Stokes Cleveland DVA Medical Center
VZV	varicella zoster virus
HZ	Herpes Zoster
CMI	cell mediated immunity
ZOSTAVAX	Trade name for the shingles vaccine
XRT	X-Ray Therapy
chemo	chemotherapy

8. Provide a BRIEF SUMMARY of the background for this research. DO NOT CUT and PASTE paragraphs that do NOT summarize the background.

- *Include a critical evaluation of existing knowledge, and specifically identify the information gaps that your protocol is intended to fill.*
- *Refer to appropriate citations in the scientific literature and include your references at the end of this section.*
- *Include the rationale for conducting the research at the VA.*

The incidence of Herpes Zoster (HZ), caused by reactivation of VZV from sensory nerve ganglia, rises markedly after the sixth decade of life or as a result of impaired cell-mediated immunity (CMI). There are an estimated one million cases of herpes zoster in the United States annually [1]. ZOSTAVAX was approved by the FDA in 2006 [2] for immunocompetent adults over the age of 60 after the Shingles Prevention Study demonstrated efficacy at 51% [3] and in 2011 for adults over the age of 50 after a randomized controlled trial in 50-59 year olds demonstrated efficacy at 69.8% [4]. The Center for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommends the vaccine for immunocompetent adults over the age of 60.

The risk of HZ increases with age and among those with impaired immunity. VZV infections continue to represent a significant source of morbidity among patients with cancer. In population based studies, cancer has been identified as the most common risk factor for the development of HZ infection [5, 6]. While those with hematologic malignancies, particularly those receiving hematopoietic stem cell transplant bear the greatest burden of HZ, individuals with solid organ tumors remain at significantly increased risk of zoster compared to general population. In another large study of 14,670 cancer patients compared with incidence rates of HZ reported in a general US population, the age- and sex-standardized rates of HZ was 1.9 times higher in those with solid tumors [7]. Another study found a two-fold increased risk of HZ from baseline in this population and further increase in risk to three-fold among those receiving chemotherapy with a median age at infection of 59 years [5]. In a study that investigated VZV infections in solid tumor patients undergoing chemotherapy, the incidence was 2.2% for patients receiving adjuvant chemotherapy and 6.2% in those undergoing palliative chemotherapy [8]. In one population based study the median time from the completion of chemotherapy to the onset of infection was less than one month [9]. Not only does HZ occur more frequently in individuals with impaired host defense mechanisms, they are also more likely to have disseminated disease and complications than immunocompetent hosts [7, 10].

Although ZOSTAVAX was approved in 2006 for prevention of herpes zoster in healthy, immunocompetent individuals, there is insufficient data regarding this vaccine in immunocompromised persons. The ACIP recommends the use of ZOSTAVAX in solid tumor patients anticipating immune suppression at least 14 days before initiation of immunosuppressive therapy [1]. Unlike other vaccines, VZV vaccine is intended to protect against reactivation of latent infection and the primary mechanism of protection is through enhancement of cell mediated immunity (CMI) rather than humoral immunity. Individuals at greatest risk of the disease such as those about to be immunocompromised due to chemotherapy may also have the most impaired immune responses to the VZV vaccine. Determining the immunologic efficacy of ZOSTAVAX and the durability of CMI after chemotherapy in this population is the topic of this study.

There is a substantial history of shingles vaccine studies in the VA system. The main study that was used the FDA approval was a large VA cooperative study [3]. We also have substantial numbers of oncology patients of the appropriate age range so this study is well suited to the veteran population and of need clinically.

References

1. Harpaz R, Ortega-Sanchez IR, Seward JF, Advisory Committee on Immunization Practices Centers for Disease C, Prevention: Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control 2008, 57:1-30; quiz CE32-34.

2. https://www.merck.com/product/usa/pi_circulars/z/zostavax/zostavax_pi2.pdf

3. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, Arbeit RD, Simberkoff MS, Gershon AA, Davis LE, et al: A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. The New England journal of medicine 2005, 352:2271-2284.

4. Schmader KE, Levin MJ, Gnann JW, Jr., McNeil SA, Vesikari T, Betts RF, Keay S, Stek JE, Bundick ND, Su SC, et al: Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2012, 54:922-928.

5. Chen SY, Suaya JA, Li Q, Galindo CM, Misurski D, Burstin S, Levin MJ: Incidence of herpes zoster in patients with altered immune function. Infection 2014, 42:325-334.

6. Ragozzino MW, Melton LJ, 3rd, Kurland LT, Chu CP, Perry HO: Population-based study of herpes zoster and its sequelae. Medicine 1982, 61:310-316.

7. Habel LA, Ray GT, Silverberg MJ, Horberg MA, Yawn BP, Castillo AL, Quesenberry CP, Jr., Li Y, Sadier P, Tran TN: The epidemiology of herpes zoster in patients with newly diagnosed cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2013, 22:82-90.

8. Kim ST, Park KH, Oh SC, Seo JH, Shin SW, Kim JS, Kim YH: Varicella zoster virus infection during chemotherapy in solid cancer patients. Oncology 2012, 82:126-130.

9. Rusthoven JJ, Ahlgren P, Elhakim T, Pinfold P, Reid J, Stewart L, Feld R: Varicella-zoster infection in adult cancer patients. A population study. Archives of internal medicine 1988, 148:1561-1566.

10. Schimpff S, Serpick A, Stoler B, Rumack B, Mellin H, Joseph JM, Block J: Varicella-Zoster infection in patients with cancer. Annals of internal medicine 1972, 76:241-254.

11. Weinberg A, Zhang JH, Oxman MN, Johnson GR, Hayward AR, Caulfield MJ, Irwin MR, Clair J, Smith JG, Stanley H, et al: Varicella-zoster virus-specific immune responses to herpes zoster in elderly participants in a trial of a clinically effective zoster vaccine. The Journal of infectious diseases 2009, 200:1068-1077.

9. Provide a BRIEF SUMMARY of the purpose and scientific rationale for this research. DO NOT CUT and PASTE paragraphs that do NOT summarize the purpose and scientific rationale.

- *State clearly, in terms a non-scientist/non-medical person can comprehend, what you expect to learn from the study and the specific hypothesis (es) to be tested.*

- *The objectives should be stated in such a way that the reader can determine the appropriateness of the study design.*

Clinical Hypothesis

1. We hypothesize that individuals with solid organ tumors receiving ZOSTAVAX at least 14 days prior to initiation of chemotherapy or surgery and then chemotherapy will have a consistent immunologic benefit over time (from chemotherapy initiation to on chemotherapy to 3-6 months post chemotherapy) as compared to those individuals who did not receive the vaccine but had the same oncology treatments.
2. We hypothesize that the fold increase in Varicella Zoster Virus (VZV)-specific immunity in subjects with solid organ tumors that were given ZOSTAVAX at least 14 days prior to initiation of chemotherapy will be higher than the control group that is not vaccinated.
3. We hypothesize that immediately before the second cycle of chemotherapy VZV-specific immunity will be higher in those subjects that received ZOSTAVAX prior to chemotherapy than those that were not vaccinated.
4. We hypothesize that at 3-18 months post-chemotherapy VZV-specific immunity will be higher in those subjects that received ZOSTAVAX prior to chemotherapy than those that were not vaccinated.
5. We hypothesize that ZOSTAVAX is safe if given to subjects with solid organs tumors at least 14 days prior to initiation of chemotherapy or surgery followed by chemotherapy.

10. Describe the means of analyzing the data and evaluating the results.

- *State the anticipated methods to be used for analysis and interpretation of the data.*

- *The methods must compliment the design of the study and the nature of the data which is being collected.*

Fold change will be the primary immune analysis and will be calculated for each individual subject based on their day 0 spot forming units on ELISPOT assay. Fold change will be calculated at each time point (chemo initiation, during chemo, 3 months post). This will take place in both the vaccinated and control (non-vaccinated) groups. The control group will have responses measured as well and is the essential comparison group to see how the responses change in relation to the vaccinated group through the pre, during, and post chemotherapy time points. As this model reflects a 2 group by 3 time point design, our initial overall assessment of the data will use a 2X3 Repeated Measures ANOVA (RMANOVA) to identify mean differences between groups, within time mean differences, and the interaction between groups and time to identify if the trends in the means over time is different for groups (vaccine vs. no vaccine). For the next step to gain a better understanding of how well the vaccine works at each time point (Hypothesis 2-4), we will use independent samples t-tests to analyze group mean differences at each time point separately to gain a better understanding of how the groups may be different at chemotherapy initiation, during chemotherapy, and at 3-24 months post-chemotherapy. Additionally, if we identify a significant interaction between group and time points, we will run follow-up RMANOVAs for each group separately to identify not only mean difference over time, but also linear (e.g. a steady increase or decrease in mean scores over time) and quadratic (e.g. a high mean scores at chemotherapy initiation, followed by a decline in mean score during chemotherapy, followed by a steady increase in mean score at 3-24 months post-chemotherapy) trends in the

means over time for each group. Violations of the assumptions for each analysis will be tested and the data will be transformed or the nonparametric equivalence analysis will be used when appropriate.

We will also perform multiparameter flow cytometry analysis on the cells to measure in greater detail what subtypes of T cells are responding. If there are sufficient PBMC available we will perform transcriptomic analysis of vaccine-induced gene changes over the time course of the study. Antibody titers may also be assessed as they are of historical interest in zoster and there is significant data on changes in antibody titers as at least a measure of immunologic response.

A portion of the sample may be sent to our collaborators at University of Pennsylvania (Drs. Michael Betts and John Wherry), or Vaccine and Gene Therapy Institute in Port-St-Lucie, FL (Dr. Rafick Sekaly, coming to CWRU this Fall to join our faculty), and Merck's immune assay unit (Swiftwater, PA) as each of these collaborators perform assays that we do not perform at the VA in the Canaday laboratory. Any samples that are sent will be coded with no personal identifiers. The cells going to Penn will have advanced T cell marker analysis and cloning, to Dr. Sekaly they will have transcriptomic analysis, and to Merck they will have anti-VZV glycoprotein ELISA performed. Samples will be destroyed in Cleveland and at the other sites after the assays are performed.

11. Provide a BRIEF DESCRIPTION of how the estimated number of study subjects needed for this research was determined

- *If this is a quantitative study provide the method of determining sample size estimates.*
- *If multiple studies are planned provide a power analysis or justification for each one.*

This is a pilot study so precise sample size calculations are not possible since the data do not exist yet to determine this. Obtaining this pilot data is one of the key purposes of this study. For the primary analysis: If we anticipate some loss of subjects for various reasons beyond our control so that we hope to end up with about 76 subjects for full analysis after initially enrolling 90 subjects. This is based a projection of receiving up to 30 coded samples from our collaborator Ken Schmader at Duke University who is running a similar study at that site and initially enrolling 60 from Cleveland. Using G*Power to perform a sample size calculation with 76 subjects (38 vaccinated and 38 un-vaccinated assuming some loss due to lack of all 4 timepoints) and an analysis comparing these two groups at the 3 time points to test Hypothesis 1 using a 2 x 3 Repeated Measures ANOVA with power 0.8 and α error 0.05 we can detect an effect size of 0.27. For independent t-tests analyzing mean differences at each individual time point we would be able to detect an effect size of 0.58. For both of these types of analyses our power is near a medium effect size. The data from this pilot study will inform the sample size for a larger future study.

12. The research involves the following procedures conducted by and for what purpose:

PROCEDURE	PERFORMED BY:		PROCEDURE IS:	
	Research Staff	LSCDVAMC Clinical or Support Staff	Standard of Care*	For Research Purposes Only**

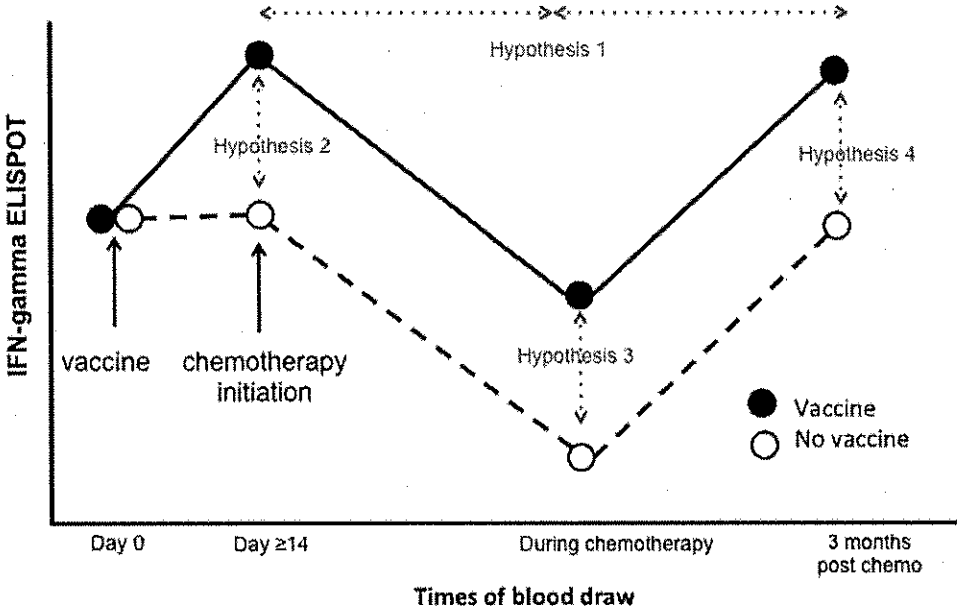
PROCEDURE	PERFORMED BY:		PROCEDURE IS:	
	Research Staff	LSCDVAMC Clinical or Support Staff	Standard of Care*	For Research Purposes Only**
Audiotaping / Videotaping *Attach VA Form 10-3203* **REQUIRED ONLY FOR IN-PATIENT AND OUT-PATIENT SUBJECTS**	☐	☐	☐	☐
Biopsy	☐	☐	☐	☐
Blood collection	☒	☐	☐	☒
Chart review – prospective (FOR pre-SCREENING)	☒	☐	☐	☐
Chart review – retrospective	☒	☐	☐	☒
Review of existing data (ex: registry, Database , etc.)	☐	☐	☐	☐
X-ray or Ionizing radiation exposure	☐	☐	☐	☐
Clinical Tests	☒	☐	☐	☒
Device implantation	☐	☐	☐	☐
Drug administration	☒	☐	☐	☒
EEG, EKG , ECG…etc	☐	☐	☐	☐
Gene therapy, Genetic analysis	☐	☐	☐	☐
Pregnancy/Breastfeeding Screening	☐	☐	☐	☐
Interview, Questionnaire, Diary, Survey *(please attach)*	☒	☐	☐	☒
Stool collection, Urine collection, or any Non-surgical Specimen collection	☐	☐	☐	☐
Surgical procedure or Specimen removal during surgery	☐	☐	☐	☐
Tissue banking *(complete Section 12)*	☐	☐	☐	☐
Use of pre-existing tissues/specimens	☐	☐	☐	☐
Other *(list)*:	☐	☐	☐	☐

- **Standard of care procedures are procedures performed in the course of normal medical care.*
- ***Research Procedures are performed for the purposes of this research alone.*

13. Please describe the research design and all study related procedures.

- *Describe **ALL PROCEDURES ASSOCIATED WITH THIS RESEARCH**. This includes standard of care and research procedures.*

- *For complex studies please include diagrams and tables. Be sure to describe when each procedure will be performed. Be sure to provide information for **each cohort, including normal controls**).*



Study participants based on the inclusion and exclusion criteria listed below will be recruited from the Oncology clinics and medical services of the Cleveland VA. The study oncologist will review the study with them. Subjects that consent will be randomized to one of the two arms, vaccine or no vaccine. Individuals will undergo blood draws for immunologic assays according to time points depicted in the figure below. Each blood draw (25 ml each) has been timed to follow routine clinical monitoring as ordered by the oncologist for maximum feasibility.

- The first blood draw will be at the time of consent into the study. We anticipate this time to be the first visit with the oncologist. They will receive ZOSTAVAX on that day if they are in that arm of the study.
- The second blood draw will be on the day of chemotherapy initiation, no earlier than 14 days post-vaccination. This will be longer than 14 days for example when there is surgery between the vaccination and the start of chemotherapy.
- The third blood draw will be at the start of the second chemotherapy cycle.
- The fourth blood draw will be 3-24 months post chemotherapy cessation. The timing of the final blood draw is based on cessation of chemotherapy and not any concurrent radiation therapy that would be also completed by the 3-6 month post-chemotherapy sampling.

The subjects chemotherapy is decided by the Oncologist and/or Tumor Board in consultation. The duration of chemo similarly is also decided clinically. If the patient needs surgery or XRT

as part of the therapy, it is decided on entirely by the clinicians. The study is working around all of these clinical decisions.

Subjects will be called between visit 2 and 3 and then between visits 3 and 4. They will be asked if they had a side effects or event that may have been serious since the last study visit or telephone contact. They will also be asked if they were exposed to anyone who has chickenpox or shingles, and if they had any symptoms of shingles.

For 4 weeks after they receive their shot, they will be asked to record information about potential vaccine side effects on the vaccination Report Card.

14. Will the research involve the following?

☐ **N/A** **Chart/Data Review**

Placebo Group	☒ **No**	☐ **Yes** *(describe)*:
Other Control Group	☐ **No**	☒ **Yes** *(describe)*: The control group is persons that do not get the vaccine.
Randomization	☐ **No**	☒ **Yes** *(describe)*: We will obtain clinical information to determine eligibility this includes meds and PMH and then follow the subject's clinical course to know when to do the subsequent sampling. We will use a cloud based randomized tool to generate the list before the start for the whole study for what the order of vaccine or no vaccine will be. We will then have paperwork packets in the order of enrollment premade. We will open each packet at the consenting time and find vaccine or not and enroll and begin the study.
Deception	☒ **No**	☐ **Yes** *(describe)*:

15. Does the research involve the use and/or disclosure of Individually Identifiable Health Information in any form or medium?

☐ **No** ☒ **Yes** **If yes, complete the required HIPAA Waiver/Authorization forms.**

16. Does the study include the administration of a study agent that does not require FDA approval and does not require an IND (e.g. vitamins, food supplements, isotope tracers, alternative medicines, etc.)?

☒ **No** ☐ **Yes** *-provide a detailed description of the procedures used to assure patient safety:*

17. Will radioactive material be administered or will subjects be exposed to ionizing radiation?

- *Ex. Radiographic equipment, fluoroscopic equipment, and CT scanners, etc.*

☒ **No** ☐ **Yes**

18. In your judgment, could the objectives of the research be met in a way that presents less risk to subjects?

☒ **No** ☐ **Yes** *please explain*:

Section 4 – Subject Selection, Recruitment, and Vulnerable Populations

19. Anticipated duration of entire study reported in years: 5

20. Estimated number of subjects to be studied at the LSCDVAMC or charts/records to be reviewed.

- *Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,)*:

30 ZOSTAVAX
30 no vaccine

21. Estimated number of subjects to be studied or charts/records to be reviewed at all sites

- *Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,)*

30 ZOSTAVAX
30 no vaccine
The Duke University site will have 15 ZOSTAVOX and 15 no vaccine

N/A SINGLE SITE ☐

22. Duration of individual subject participation

*Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,).* 5 years or less depending on the duration of their chemo.

Chart/record review ☐ **N/A**

23. Age range of subjects

- *provide answers for **each cohort**, including normal controls*:

☐ **Adults 18 years or greater**

☒ **Specific age range** (list age range): 50 years and older for both cohorts

☐ **Children –waiver from VACO:** ☐ **attached** ☐ **pending-** ***provide submission date:***

***Contact AO/Research holly.henry@va.gov for guidance..*

24. Which of the following will be recruited or reviewed for this study *(check all that apply)***?**

☒ **Veteran Inpatients**
☒ **Veteran Outpatients**
☐ **Veteran Families**
☐ ***Normal volunteers**
☐ ***Non-Veterans; Provide justification**

☒ **Men**
☒ **Women**

*According to VHA Handbook 1605.04 Notice of Privacy Practices VHA must provide a copy of its VHA Notice of Privacy Practices to all non-Veteran patients (e.g., active duty personnel or those seeking care in humanitarian circumstances) receiving care or treatment at a VHA health care facility or non-Veteran research subjects enrolled in an approved VHA research study with clinical trials. VA Form 10-0483 Acknowledgement of the Notice of Privacy Practices should be signed by the non-Veteran research subject at the time of consent and given a copy of the Notice of Privacy Practices. Once the Acknowledgement Form is signed please send a copy to the Privacy Officer. If additional information is needed please contact your Facility Privacy Officers Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / phone 8214101.

25. Which vulnerable population(s) will be TARGETED for recruitment in this study:

- *Indicate only those populations that are specifically targeted for the research described in this document.*
- ***It is not necessary to check any box if, for example, your study will include a full range of subjects, some of whom may be elderly or subjects who might incidentally be employees.***

☐ **N/A Chart Review** (*proceed to Item 30*)

☒ **NONE** (*proceed to Item 26)*

☐ **Medical students, house staff, or Employees of the VAMC or Case**

☐ **Pregnant Women OR Women who are Breastfeeding, Human Fetuses, or Neonates**

☐ **Children – Complete Section 14 "Children as Research Subjects"**

☐ **Prisoners (The LSCDVAMC does not conduct research involving prisoners)**

☐ **Targeting Persons over Age 65**

☐ **Persons with Acute/Severe Mental/Physical Disabilities** *(describe)*:

☐ **Persons with Cognitive, Social, Economic, or Educational Disadvantages** *(describe)*:

☐ **Others** *(describe)*:

a. Provide the Scientific and Ethical reasons for Targeting these vulnerable populations in the research:

b. What additional safeguards or provisions will be used to protect the rights and welfare of the identified targeted vulnerable subjects?

☐ **Surrogate consent**

☐ **Subject assent**

☐ **Use of a consent or Medical monitor**

☐ **Use of a waiting period**

☐ **A patient advocate will participate in the informed consent process**

☐ **Key elements of informed consent will be presented orally**

☐ **No supervisor or rater will be involved in obtaining consent**

☐ **Other - Describe Additional safeguards you plan to use:**

c. Describe the procedures used to ensure that the subject's legally authorized representative is well informed regarding his/her role and obligation to protect persons with impaired decision making capacity:

26. Procedures for Recruiting Subjects -check all that apply and attach all recruitment materials:

☐ **Not Applicable**

☐ **Materials; Recruitment Letter, Posting on Bulletin Board, Brochure, Flyer, Post card, etc.**

☐ **Media; Internet Ads, Press Releases, Newspaper, Radio**

☒ **Investigator's Patient Population**

☒ **Physician Referral**

☐ **Letters to Physicians/Clinicians**

☐ **Other** *(describe)*:

27. Will VA computer systems be used to identify potential subjects?

- *e.g. VISTA, CPRS, Pharmacy Databases, other clinical databases, etc,*

☐ **No** ☒ **Yes- Describe how the computer will be used to identify patients. List all systems used and all information to be collected:** We will request a HIPAA waiver so our coordinator can help the oncology staff identify potential canidates for the study. We will review the charts of the future clinics and inpatients anticipating chemo in CPRS to do a prescreen of subjects for eligibililty to the study. This information will then be communicated to the study oncology providers prior to their clinic appointment or inpatient discharge.

28. Will subjects be identified and/or recruited in clinics and/or inpatient wards at the LSDCVAMC?

☐ No ☒ Yes- **explicitly describe your process for identifying and/or recruiting these patients:** *(address all cohorts):* See the answer for question 27. We will focus on subjects with recent cancer diagnosis that will be seen in the clinics of oncology or by their inpatient team. We can assit the oncologists in prescreening for suitability to the study. Also the coordinator and Co-I may discuss with the medical teams about our study that we are searching for subjects with oncology diagnosis that will receive chemo soon and the primary providers then may refer subjects to us to screen.

29. In addition to the consent form will any other materials be given to the subject?

☐ **N/A Chart/data review**

☐ **No** ☒ **Yes- check all that apply and submit for IRB review:**

☐ **Letter**

☐ **Information Sheets**

☒ **Questionnaire, Survey, Diary**

☐ **Other** *(flyer, brochure, describe):* If they enroll they will fill out the vaccine report card.

30. Please list by bullet point inclusion/exclusion criteria for the study.

- *Entry criteria should be as detailed as necessary to define the subject population(s) under study and reduce confounding design. Include precise criteria for age, gender, and other relevant factors.*
- *List specific exclusion criteria which could interfere with the study design or place a subject at risk during the study.*
- *Provide answers for **each cohort**, including normal controls.*

Inclusion criteria:

- Solid organ tumor patients that have at least 14 days between entry into the study with ZOSTAVAX vaccination and initial therapy for their malignancy that will include chemotherapy alone or surgery with subsequent chemotherapy plus or minus radiation therapy.
- A plan for chemotherapy that at the onset at least has an anticipated stop date within 3-6 months of our sample collection phase of the study.
- Age 50 or older

Exclusion criteria:

- Prior history of HZ or shingles vaccine
- Systemic chemotherapy <3 months pior to enrollment
- Any history of hematologic malignancy, HIV/AIDS, hematopoietic stem cell transplant, or other cellular immunodeficiency state
- Those receiving immunomodulating drugs at the time of vaccination such as prednisone methotrexate, azathioprine, mercaptopurine, or other biologics including TNF-α inhibitors
- Widespread metastatic tumor with bone marrow involvement
- Indefinite duration palliative chemotherapy subjects
- Inability to communicate with the study staff or being unable to consent for themselves.
- History of anaphylactic/anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine.

☐ **N/A Chart/data review**

31. By role, (PI, Coordinator, etc.) who will assess for eligibility and how will this be accomplished?

PI, Co-I and/or Coordinator after we have a waiver exemption will prereview subjects in CPRS to determine eligibility. We will examine the medical issues for inclusion and exclusion. We will also look for any discussion or diagnosis that showed or suggested lack of capacity to consent as we will only enroll those that can consent for themselves.

32. Are any subjects excluded on the basis of race, ethnic group, understanding of English, socioeconomic status, education, gender, or pregnancy?

- *Note: It is appropriate to indicate that you do not anticipate encountering potential subjects who do not speak English* ***based on the population to be studied***

☐ **No** ☒ **Yes** - *(provide justification)*: If a subject does not speak English we do not feel we can consent them properly and follow then for adverse reactions to the vaccine for example.

☐ **N/A Chart/data review**

33. Will subjects be reimbursed or paid an incentive for participating?

☐ **No (skip to item #35)** ☒ **Yes**

☐ **N/A Chart/data review (skip to item #38)**

34. How and when will they be paid?

☐ **Cash** ☐ **Check** ☒ **Other** -please explain: VISA card will be used if we are not able to work out a mechanism for cash with the VA Foundation. Dr. Canaday had a discussion with Jeff Moore from the VA Research Foundation on 7-11-14 regarding this topic. Dr. Moore is not aware of a way they can do cash at this moment. It be an option in the future and we could then use this rather than a preloaded VISA.

☒ **Prorated** -provide schedule: $20 per blood draw and $20 additional for travel costs for the final blood draw if it does not correspond with a routine visit for care that is already scheduled. ☐ **Fixed** -provide schedule

35. Will subjects be responsible for any of the costs related to the research?

☒ **No** ☐ **Yes**- please explain:

36. Will treating physicians, clinicians, or researchers be compensated or paid an incentive for referring or enrolling subjects?

☒ **No** ☐ **Yes** -please explain:

37. Please describe steps you will take to ensure that subject selection is fair and equitable:

We have very objective exclsuion criteria so that should allow for fair recruiting.

Section 5 – Risks and Benefits

38. Please list by bullet and describe the reasonably foreseeable physical, psychological, social, economic, and privacy risks, side effects, or discomforts associated with the research and their expected frequency and severity.

- *If this study is a retrospective chart review, or involves only the analysis of data, risk may still be present in the form of data security concerns.*

Some reported risks of ZOSTAVAX include:

o Injection site reactions such as: local redness, swelling, pain and tenderness, itching, bruising, and warmth.

o Headache

o Fever

o Allergic reaction, which may be life-threatening

- o Rash, which may resemble chickenpox
- o Swollen glands near the injection site (may last a few days to a few weeks)
- o Joint pain
- o Muscle pain

These reactions are either rare or mild in severity making this a safe vaccine with very few exclusions by the FDA.

Blood samples: drawing blood from your arm may cause pain, bruising, lightheadedness, and rarely, fainting or infection.

Loss of privacy is always a risk with any study. We are not collecting those most sensitive topics of information and we will code the sample as soon as they are enrolled so these risks are minimal.

***Certificate of Confidentiality:**

- Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure.
- They allow the investigator and others who have access to research records to refuse to disclose identifying information on research subjects in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.
- Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.
- By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to subjects.
- **For more information, see http://grants1.nih.gov/grants/policy/coc/index.htm.**

39. Is this project principally concerned with the collection of sensitive information such as sexual attitudes, use of drugs or addictive products, and illegal conduct that would need to be protected against subpoena or forced disclosure in order to protect subjects?

☒ No

☐ Yes- will an application for a *Certificate of Confidentiality be submitted to the National Institute of Health upon IRB approval (or approval contingent on the issuance of such a certificate)?

☐ Yes ☐ **No provide a justification as to why a Certificate of Confidentiality will not be obtained:**

40. Describe all procedures that minimize risks, please include study and standard of care procedures:

We will screen the subjects carefully for any contraindications to the vaccine. Administration of the vaccine will be performed by trained and experienced personal either on the study staff or the clinical nursing staff that gives this standard of care vaccine. Blood draws also will be obtained by the study staff or trained clinical staff. In terms of privacy, interactions with the subjects will occur in private.

41. Describe alternative procedures or course of treatment, if any, which might be advantageous to the subject. State if no alternatives exist or if this is not a treatment study.

The only alternative is not to receive the vaccine and defer it until later from their primary provider.

Minimal Risk: Minimal risk means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

42. Please give your overall risk classification for the research:

☐ **Minimal Risk**

☒ **Greater than Minimal Risk**

43. Will subjects receive any direct benefit from this research?

☐ **No** ☒ **Yes** -describe the direct benefits: They may get benefit from receiving the shingles vaccine that would protect them from an acute zoster outbreak.

44. Please explain briefly why you consider the risks associated with the study to be reasonable in relation to its benefits?

We believe the risks of this FDA approved vaccine are minimal but they do not exactly meet the very strict definition of minimal risk provided above in the yellow box. ZOSTAVAX is an attenuated live virus vaccine so it is not part of "routine physical or psychological examination or test" rather it is something being given. We are using it in accord with the FDA package insert however. Also it is a very safe and low risk vaccine as well. We will carefully review the subjects for contraindications to further minimize any risk.

Section 6 – Informed Consent

45. Type and number of Consent-

- *When more than one consent form is being used a descriptor MUST be in the header section describing the population and/or phase of the study*:

☒ **Written Informed Consent –number used in this study** 1

☐ ***Oral Script/Letter/Information Sheet- number used in this study** ***Submit Request for Consent Waiver Form-waiver of documentation of informed consent**

☐ **No informed consent at all in this study- Submit a Request for Consent Waiver Form-waiver of informed consent and proceed to item 53**

46. Will all adult subjects have the capacity to give informed consent?

☒ **Yes** ☐ **No- Describe range of impairment.**

- *Research involving more than minimal risk, capacity should be determined by a psychiatrist, clinical psychologist, or other qualified professional not otherwise involved in the research.*
- *Individuals who lack the capacity to consent may participate in research only if a legally authorized representative gives consent on their behalf.*

We will review the medical record and if there is concern about the subject's capacity we will talk with the subject's primary physician and team to help us assess their capacity. Many older

persons in particular already have evaluations on the chart discussing capacity. It is not feasible for us to send all subjects for a capacity evaluation and still meet the strict time parameters of 14 days between vaccination and treatment.

47. Will anyone other than the subject be authorized to provide consent or permission for the subject's involvement in the research?

- *e.g., parents, court ordered guardian, spouse, etc.*

☒ **No** ☐ **Yes** -please explain:

48. Describe <u>how</u> and <u>where</u> informed consent will be obtained:

Consent will be obtained in the VA exam room or hospital room of the subject. The subject will be given the consent and have time to read it. They will also have the study explained and allow time for the study staff to answer questions. The research team will then question the subject about the key elements of the study to assure they understand it.

49. Will there be an opportunity for potential subject to take the consent form home to discuss participation and options with family members?

☐ **Yes** ☒ **No** - please explain:

It is not possible to take the consent home in virtually all cases as the subject will not have sufficient time to fit into the 2 week time window between the shot and chemotherapy if they take the consent home.

50. List by role who will be obtaining informed consent from subjects or their legally authorized representatives:

- *ex. study coordinator, co-investigator, research nurse, research assistant, PI*

All members of the study team are authorized to obtain consent.

51. Please describe how informed consent will be obtained from subjects who do not read or understand English;

- *identify any languages likely to be encountered, and attach a copy of a translated and authenticated informed consent document*
- *It is appropriate to indicate that you do not anticipate encountering potential subjects who do not speak English based on the population to be studied*

We will exclude those that do not understand English. If they cannot read we can read the whole consent to them.

52. Describe who *(by Role ex. PI, Coordinator, etc.)* **and how it will be determined that subjects and/or legally authorized representative understand the research and their rights.**

- *ex. question and answer, repeat back parts of the research, describe a procedure...etc*

Any member of the study team is able access this. The study staff will explain the study when consenting the subject and then go over key elements and have the subjects describe back what they understand will happen in the study.

Section 7 – Privacy and Confidentiality

Privacy - refers to a person's desire to control the access of others to themselves. For example, persons may not want to be seen entering a place that might stigmatize them, such as a pregnancy counseling center that is clearly identified as such by signs on the front of the building. Privacy concerns people, whereas confidentiality concerns data. The research proposal should outline strategies to protect privacy including how the investigator will access information about potential subjects.

In developing strategies for the protection of subjects' privacy, consideration should be given to:

- Methods used to identify and contact potential subjects
- Settings in which an individual will be interacting with an investigator
- Appropriateness of all personnel present for research activities
- Methods used to obtain information about subjects and the nature of the requested information
- Information that is obtained about individuals other than the "target subjects," and whether such individuals meet the regulatory definition of "human subject" (e.g., a subject provides information about a family member for a survey)
- How to access the minimum amount of information necessary to complete the study

Confidentiality - methods used to ensure that information obtained by researchers about their subjects is not improperly divulged. Confidentiality refers to the researcher's agreement with the subject about how the subject's identifiable private information will be handled, managed, and disseminated. The research proposal should outline strategies to maintain confidentiality of identifiable data, including controls on storage, handling, and sharing of data. When appropriate, certificates of confidentiality could be used to maintain the confidentiality of identifiable data

When the IRB evaluates research proposals for strategies for maintaining confidentiality, where appropriate, consideration will be given as to whether:

- Methods to shield subjects' identity adequately protect subject privacy
- There is a long-range plan for protecting the confidentiality of research data, including a schedule for destruction of identifiers associated with the data
- The consent form and other information presented to potential research subjects adequately and clearly describe confidentiality risks.
- The informed consent process and the informed consent document, and if applicable the Authorization Form, clearly delineates who will have access to the subject's information and under what circumstances data may be shared (i.e., government agencies, sponsors).

53. Describe when and where subjects will provide their information. Include the nature of the information and who will receive and use the information. Document the provisions used to protect privacy interests of those subjects when gathering their information and data.

We will obtain the information from CPRS and from the subjects in an exam room or hospital room. We will obtain birthdate, PMH, and information on how to contact the person as the study is ongoing. The link to the code will be stored in a password protected file behind the VA firewall and in paper form in a locked cabinet in a locked room.

54. Will researchers have access to identifiable private information about potential subjects <u>outside</u> of this research project? *Ex. PI is provider who has access to medical records for clinical care*

☐ **No** ☒ **Yes- please explain:** The oncology CO-I's on the study are providers for the subjects.

55. Will Researchers collect identifiable private information on anyone other than the subject?

- *Ex. family members, friends, colleagues, classmates...etc.*

☒ **No** ☐ **Yes -please explain:**

56. At the time data are transcribed or recorded for this study they are?

☐ **Fully identifiable- list identifiers to be collected:**

☒ **Coded with a unique identifier- describe the code:** It will be a few letters and numbers. We will not use the subjects S.S. number, birth date or initials for the code.

a. Who will have access to the key? All of the study team.

b. Where is the key maintained? Two locking barriers must be in place between the coded data and the key. We will have a password protected file behind the VA firewall and also a written backup stored in a locked drawer or cabinet in the oncology office area initially as the enrolment is ongoing and then for long term moved to Dr. Canaday's lab in K203.

☐ **De-identified-by Privacy Officer or Statistician.**

☐ **Other** *(describe)*:

57. How will electronic research data be secured while the study is active?

☐ **No electronic data will be stored**

☐ **VA encrypted laptop**

☐ **Encrypted VA device/media- describe:**

☒ **VA network drive;**

☐ **M: drive; whose?**

☒ **S: drive**

☒ **Folder access password protected**

☐ **Other drive location** *(for example P: drive)*:

☐ **Folder access password protected**

58. How will hardcopy research data be secured while the study is active? Two locking barriers must be in place.

☐ **No hardcopy data will be stored**

☒ **Locked office and locked file cabinet**

☐ **Data coded by PI or study staff with a master list secured and kept separately**

☐ **Data de-identified by Privacy Officer or Statistician-** *(***VA does not consider coded data to be de-identified)**

☐ **Other -specify:**

59. Provide the physical location including room number (and address if outside of this VA) where all electronic and hardcopy data will be stored: A locked cabinet in the oncology office area (Dr. Singh's office) and/or in Dr. Canaday 's lab K203 in a locked cabinet.

60. Is identifiable information physically or electronically sent <u>TO</u> the LSCDVAMC from other institutions or locations?

☒ **No** ☐ **Yes** - contact Privacy Officer Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / 8214101 or Information Security Officer Bruce Frankford bruce.frankford@va.gov / phone 821 1604 – prior to submitting to the Research Service.

****If yes complete the following:**

a. LSCDVAMC investigator will receive:

☐ **Hardcopy information or specimens**

☐ **Electronic information**

b. What are the procedures for transporting and/or transmitting identifiable information securely?

c. What will be the final disposition of the identifiable data transferred to the LSCDVAMC?

- **Record Control Schedule 10-1 indicates that all research records must be retained indefinitely**

61. Is identifiable information physically or electronically sent FROM the LSCDVAMC to other institutions or locations?

☒ **No** ☐ **Yes** contact Privacy Officer Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / 8214101 or Information Security Officer Bruce Frankford bruce.frankford@va.gov / phone 821 1604 – prior to submitting to the Research Service

****If yes complete the following:**

a. The LSCDVAMC investigator will send:

☐ **Hardcopy information or specimens**

☐ **Electronic information**

b. What are the procedures for transporting and/or transmitting identifiable information securely?

c. What will be the final disposition of the identifiable data transferred offsite?

- **Record Control Schedule 10-1 indicates that all research records must be retained indefinitely**

Records will be maintained indefinitely or until the RCS-10 is updated.

62. Record Control Schedule 10-1 indicates all research records must be retained indefinitely. Please indicate where this information will be stored and the safe guards to protect it:

a. Electronic Safeguards:

☐ **No electronic data will be stored**

☐ **VA encrypted laptop**

☐ **Encrypted VA device/media- describe:**

☒ **VA network drive;**

☐ **M: drive; whose?**

☒ **S: drive**

☒ **Folder access password protected**

☐ **Other drive location** *(for example P: drive)*:

☐ **Folder access password protected**

b. Hardcopy safeguards. Two locking barriers must be in place.

☐ **No hardcopy data will be stored**

☒ **Locked Office and Locked File Cabinet**

☐ **Coded by Study Staff**

☐ **De-identified by Privacy Officer or Statistician**

☐ **Other- Describe:**

Facility name, address, and room number where hardcopy or electronic data will be stored:

For long term storage the paper will go to Wade Park VA, K203, 10701 East Blvd, Cleveland, OH 44106 in a locked cabinet in Dr. Canaday's laboratory.

Section 8 – Data and Safety Monitoring –Greater than Minimal Risk Study

- For all research that is greater than minimal risk a Data and Safety Monitoring Plan must be developed.
- This is a plan to assure the research includes a system of appropriate oversight and monitoring of the conduct of the study to ensure the safety of subjects and the validity and integrity of the data.

***CHECK BOX IF THIS IS A MINIMAL RISK STUDY ☐ SKIP TO #65**

63. Safety monitoring for this greater than minimal risk project will include:

☐ **Data Safety Monitoring Board**:

☐ **Data Monitoring Committee**

☒ **Other**

- *Attach the plan or provide details including whether committee is independent from the study sponsor, how often it meets, whether written reports are available, etc*

The PI, primary Co-I's, and Coordinators of the study (Cleveland and Duke) will correspond at least monthly and review the study and vaccine report cards for any sign of increased toxicity in this population.

64. Describe the plan for on-site data monitoring by the sponsor, contract research organization (CRO), or other independent body: The sponsor will monitor the study according to

FDA and industry standards, with details of the monitoring activities to be made available to the IRB once they are available.

- **Research Office must be notified of all on-site monitoring visits.*

65. Conditions that may result in removal of subjects from the research *(check all that apply)*:

☐ **Medical condition unchanged**	☒ **Medical condition worsened**
☒ **Serious adverse event**	☒ **Intolerable complications**
☐ **Pregnancy**	☒ **Investigator's clinical judgment**
☒ **Subject withdrawal**	☒ **Subject uncooperative or noncompliant**
☒ **Study closure by sponsor or FDA**	☐ **Refusal to suspend breast-feeding**
☐ **Other-describe:**	☐ **Not Applicable**

66. If a subject withdraws or is removed from the study, describe the potential risks of early withdrawal and the procedures in place to minimize these risks:

There are no risks to early withdrawal from the study.

Section 9 – FDA-Regulated Drugs/Biologics

NOTE: If this research involves the use of <u>any</u> drugs or biologics, the study is subject to the Food and Drug Administration (FDA) regulations.

- **Documentation of FDA approval for the experimental use of these agents must be provided for review (industry sponsored protocol listing the IND number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IND for this study).**
- All drug/biologic products must be dispensed and tracked through the LSCDVAMC Research Pharmacy.
- An M.D. must be part of the Research Team for all studies that involve the use of a device or drugs.
- The LSCDVAMC Pharmacy and Therapeutics (P&T) Committee must approve: (1) Studies of investigational drugs (2) research involving an FDA-approved drug used in a non-approved manner, and (3) an FDA-approved drug, used as approved, when its use is part of a research protocol.
- **VA Form 10-9012 Investigational Drug Information Record** –must be completed for each drug being evaluated in a research study, regardless of IND status. In addition, the VA Form 10-9012 provides a listing of all authorized prescribers for the study drug(s).

67. Type of Product- check all that apply:

☐ **Not Applicable -No FDA-regulated drugs/biologics involved – Proceed to Section 10**

☐ **Drug**

☒ **Biologic or Other:** ZOSTAVAX (shingles vaccine)

68. Type of Trial *(check as applicable)*:

☐ **Phase I** ☐ **Phase II** ☐ **Phase III** ☒ **Phase IV** ☐ **NA**

Phase I Trials: Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the

side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy subjects and/or patients.
Phase II Trials: Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.
Phase III Trials: Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide adequate basis for physician labeling.
Phase IV Trials: Post-marketing studies to delineate additional information including the drug's risks, benefits, and optimal use.

69. FDA Status of Drugs/Biologics –

*** For drugs, an IND may not be necessary if ALL seven of the following conditions are met:**

1. The drug being used in the research is lawfully marketed in the United States;
2. The research is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
3. The research is not intended to support a significant change in the advertising for the product;
4. The research does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
5. The research is conducted in compliance with the requirements for IRB review and informed consent (21 CFR parts 56 and 50, respectively);
6. The research is conducted in compliance with the requirements concerning the promotion and sale of drugs (21 CFR 312.7);
7. The research does not intend to invoke 21 CFR 50.24 (Exception from informed consent requirements for emergency research).

Provide the following information for <u>each</u> drug/biologic used in this study:

Trade and Generic Name	**Manufacturer**	FDA Approved	**Product use consistent with product labeling**	**IND Required***	**IND Number**	**IND Sponsor or Holder****
ZOSTAVAX	Merck	y	Y	N		

70. **When the PI holds the IND, complete the following:

i. The PI has reviewed the Guidance on Requirements of the Sponsor and the Investigator as Sponsor

☐ **Yes**

ii. As the PI, you will comply with the regulatory responsibilities of a sponsor

☐ **Yes**

71. Drug Information for each drug listed in the protocol -check as applicable

☒ **Approved Drugs**

☐ **Not Approved**

- **Attach VA Form 10-9012 Investigational Drug Information Record for each drug used in the protocol**
- **Attach Package Insert or PDR monograph – copy ready, 8.5 x 11 for each drug listed in the protocol**
- **Attach Investigator's Brochure**

72. Provide a detailed description of how FDA-regulated drugs/biologics will be stored, secured, dispensed, administered, tracked, and returned.

The vaccine needs to be stored frozen and is resuspended by the researcher or clinical staff right before use as specified in the package insert. We will store the vaccine in the research pharmacy and can track its use from there.

Section 10 – FDA-Regulated Devices

This section should be completed for a medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device.

- An investigational device may be an FDA approved device that is being studied for an unapproved use or efficacy. This also includes an approved device that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial.
- Documentation of FDA approval for the experimental use of the device must be provided for review (industry sponsored protocol listing the IDE number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IDE for this study).

Device Risk Determination:

Significant Risk (SR) Device is an investigational device that: (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject, or (2) is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Non significant Risk (NSR) Device is a device other than a significant risk device.

The IRB is required to document the basis for risk determination based on the proposed use of a device in the research by considering the nature of the harm that may result from the use of the device. FDA has the ultimate decision in determining SR and NSR.

An M.D. must be part of the Research Team for all studies that involve the use of a device.

The Environment of Care Committee (EOC) must approve all research that involves electrically line-operated devices, which have leads or electrodes and will come in contact with human subjects.

73. Type of Product-check all that apply:

☒ **Not Applicable -No FDA-regulated devices involved – Proceed to Section 11)**

☐ **An FDA regulated device will be used BUT not with intent of studying safety or efficacy** *(Proceed to Section 11)*

☐ **Device**

74. List the device-include name and manufacturer:

75. **FDA Regulatory Status of the Device:**

☐ **FDA Approved Device**

- **A device approved by the FDA for distribution, marketing, sale to, and use by, the public for the study's indication.**

☐ **New Indication of an FDA Approved Device**

- **A device NOT approved by the FDA for distribution, marketing, sale to, and use by, the public for the indication used in the study.**

☐ **Investigational - Investigational Device Exemption (IDE)**

- **An FDA designation that permits a manufacturer to lawfully ship an unapproved device for use in a research study.**

Provide the following:

a. IDE Number:

b. IDE Sponsor or Holder:

If the PI holds the IDE, complete the following:

i. The PI reviewed the Guidance on Requirements of the Sponsor and the Investigator as Sponsor

☐ **Yes**

ii. As the PI, you will comply with the regulatory responsibilities of a sponsor

☐ **Yes**

c. FDA or Sponsor Device Risk Determination

☐ **Non-Significant Risk**

☐ **Significant Risk**

d. Attach documentation of FDA approval for the experimental use of the device (industry sponsored protocol listing the IDE number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IDE for this study).

☐ **Humanitarian Use Device (HUD)**

- **An FDA designation for a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. For more information about Humanitarian Use Devices see the HRPP SOP manual on the R&D website.**

Provide the following:

a. HUD Number:

b. HUD Sponsor or Holder:

c. Include a copy of the FDA letter granting Humanitarian Use Device (HUD) status.

☐ **510(k) Status –**

- **A device determined by the FDA to be "substantially equivalent" to an existing device that is legally marketed in the U.S. Until a 510(k) device is approved, it is still considered investigational.**

a. Provide the name of an equivalent device and sufficient documentation to justify 510(k)

76. Attach device information (i.e., brochure, device label)

77. Provide a detailed description of how FDA-regulated devices will be stored, secured, dispensed, administered, tracked, and returned.

Section 11 – Genetic Testing and Discovery of Genetic Information (DNA)

78. Does the research involve genetic testing or DNA/RNA extraction?

☒ **No genetic testing** (*Proceed to Section 12)*

☐ **Yes- complete the following:**

a. Describe the purpose of the genetic testing component of the study

- *Is it to establish risks, associations, or prevalence?*

b. Describe whether the test is a standard test already in clinical use or a new or experimental laboratory study

c. Describe the accuracy of the test

- *Sensitivity, specificity, reliability, validity, and variability*

79. Does an abnormal test result indicate that the subject:

☐ **Has a specific condition**

☐ **Is at risk for a specific condition**

☐ **May be at risk for a specific condition**

☐ **Has, is, or may be at risk for some other outcome**

☐ **Other** *(describe):*

80. Does a normal test result indicate that the subject

☐ **Is not at risk for a specific condition**

☐ **Is at a lower risk for a specific condition**

☐ **Is at a population risk for a specific condition**

81. Is there a risk of discovery of other results such as non-parentage or other genetic conditions?

☐ **No** ☐ **Yes- please explain:**

82. Will test results produce information on anyone (e.g. a first-degree relative) besides the subject?

☐ No ☐ Yes- please explain:

83. To whom and in what manner will genetic information be reported?

84. Will genetic counseling be made available to subjects?

☐ No ☐ Yes- indicate who will conduct the counseling and whether there are any additional charges:

85. Will DNA samples be stored?

☐ No ☐ Yes--describe where, how, and for how long the samples will be stored:

86. Who will own the DNA samples?

87. Will there be any subsequent analysis of the DNA samples?

☐ No ☐ Yes- describe the purpose of the subsequent analysis and whether there will be dissemination of any new information:

88. Describe how samples will be handled if the subject withdraws consent for further participation:

89. Will the samples be distributed to other investigators?

☐ No ☐ Yes- please explain:

90. Describe the provisions to maintain the confidentiality of research data, especially in cases where data can be linked to individual subjects:

Section 12 – Tissue Collection/Storage/Banking*

It is VA policy to ensure that human biological specimens, as well as the linked data collected as part of research projects conducted by VA investigators in VA facilities or approved off-site locations, are maintained at *VA approved tissue banks or VA-sponsored tissue banks.

See VHA Directive 2000-043 "Banking of Human Research Subjects' Specimens" for more information and also visit http://www.research.va.gov/programs/tissue_banking/default.cfm

Human biological specimens (specimens).

- **Human biological specimens are materials, such as blood, urine, tissue, organs, hair, nail clippings, buccal swabs or any other materials that are derived from human subjects and are**

either collected specifically for research purposes or as residual specimens from diagnostic, therapeutic or surgical procedures.

91. *Does the research involve storage or banking of human specimens or identifiable private information for use in future studies? *(check all that apply)*

☒ **No** *(proceed to Section 13)* ☐ **Yes-describe status of VA approved or VA sponsored facility:**

☐ **Storing or banking identifiable private information**

☐ **Storing or banking human specimens**

Please provide the following information:

a. What identifying information will be required?

b. What are the foreseeable uses of the specimens (e.g., research, pharmaceutical products, production of cellular lines for various uses, etc.)?

c. What is the VA approved or VA sponsored location/institution where the information and/or specimens will be stored?

d. How long will the information and/or specimens be stored?

e. Is the storage facility an on-site or off-site location?

f. Will subjects be able to request that their specimen and/or information be withdrawn from the bank or repository? *(explain)*

Section 13 – Children as Research Subjects

Research involving children must not be conducted by VA investigators while on official duty or at VA or VA-approved offsite facilities unless a waiver has been granted by the CRADO (See VHA Directive 2001-028 "Research Involving Children" for more information.

92. Do you plan to enroll children as research subjects?

☒ **No** *(Proceed to Section 14)*

☐ **Yes- Age range of subjects:**

93. Category of Research *(Check the box next to the category of research you believe your research falls under. The IRB will make a final category determination during review.)*:

☐ **Research involving minimal risk (the probability & magnitude of harm or discomfort anticipated are not greater than those ordinarily encountered in daily life or during routine physical or psychological tests.)** *(46.404)*

☐ **Research involving greater than minimal risk but of potentially direct benefit to the subject.** *(46.405)*

☐ **Research involving greater than minimal risk and no prospect of direct benefit to the subject but likely to yield generalizable knowledge about the subject's disorder or condition.** *(46.406)*

☐ **Research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting children/decisionally impaired adults.** *(46.407)*

94. Do you anticipate enrolling minors who are wards of the state?

☐ **No** ☐ **Yes**

95. Permission of parents or guardian *(check one only)*:

☐ **The permission of each child's parents or guardian will be sought unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child (required for categories 46.406 and 46.407 above in item 104).**

☐ **The permission of only one parent will be sought (acceptable for categories 46.404 or 46.405). If marked, provide justification:**

96. Assent of Children *(check one only)*:

☐ **The assent of each child who is capable of providing assent based on age, maturity, and psychological state will be sought.**

☐ **The assent of each child will not be sought because the capability of all of the children in this study population is so limited that they cannot reasonably be consulted. Explain why the capacity is so limited, e.g., age, maturity and/or psychological state:**

☐ **The assent of each child will not be sought because the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research. Explain what the direct benefit may be and why it is only available in the context of the research:**

Section 14 – Other

97. Please describe any other study procedures not referenced in the previous sections:

☐ **Not applicable**