MSK PROTOCOL COVER SHEET

PHASE II PROSPECTIVE TRIAL OF VACCINE RESPONSES IN CHILDHOOD CANCER SURVIVORS

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a prospective phase II trial to evaluate the response (seroconversion or >3 fold rise in titer) and duration of response following immunization with routine childhood vaccines. Revaccination will be initiated in patients in remission 3-24 months following completion of therapy whose CD4 cell count is >200/ul and serum IgG level is >500 mg/dl (≥ 6 weeks after last dose of IVIG). Re-vaccination will include age appropriate doses and vaccines, incorporating the combination vaccine, Pediarix, in patients <6 years of age, and the recently FDA approved vaccines Tdap (BOOSTRIX), the protein-conjugated meningococcal vaccine, Menactra, and the human papilloma virus (HPV) vaccine, Gardasil®. Titers will be obtained in all patients before vaccination and at approximately 6-9 week and approximately 1 year following vaccination.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Aims:

- To prospectively determine the response rate and duration of protective titers following revaccination with routine childhood immunizations in pediatric survivors of childhood cancer.

- To develop standardized recommendations for the revaccination of children following cancer treatment which can be prospectively tested.

Secondary Aims

- To determine whether in vitro parameters of lymphoid reconstitution correlate with response and duration of response.

3.0 BACKGROUND AND RATIONALE

It is currently estimated that by the year 2010, 1/640 young adults will be a survivor of pediatric cancer (1). Despite these numbers, there are no evidence-based guidelines for revaccination of this patient population following treatment, nor prospective trials assessing vaccine efficacy. Even at MSKCC, vaccination practices are not standardized among the various pediatric disease management teams. Pediatric patients who were appropriately vaccinated prior to their diagnosis may lose immunity to vaccine preventable diseases due to the immunosuppressive effects of chemotherapy and those diagnosed prior to completion of currently recommended childhood immunizations will likely be inadequately protected. Zignol et al. (2) evaluated the persistence of protective antibody in 192 children in remission following cancer chemotherapy. Lack of immunity to hepatitis B was found in 46% of patients and approximately 25% of patients lacked protective titers against measles, mumps, and rubella. In univariate analysis, loss of antibodies against measles, mumps, rubella was significantly associated with younger age at cancer diagnosis. In a study by Nilsson et al (3) in children with ALL, 40% of successfully treated patients lacked protection against measles and 28% lacked protection against rubella. Of 14 patients in this study who lacked immunity against measles and rubella, six failed to respond to revaccination with MMR (3). Ek et al (4) found that children with high risk ALL were more likely to lose immunity against diphtheria, tetanus, and H flu following treatment, and less

likely to respond fully to revaccination with these antigens compared to children with standard or intermediate risk ALL. Failure to respond to revaccination was associated with impaired recovery of memory B cells likely due to receipt of more intensive chemotherapy. The use of dose intensive, highly immunosuppressive alkylator-based therapy in the treatment of advanced neuroblastoma, bone and soft tissue sarcomas will likely impair the ability of successfully treated children to respond and maintain protective antibody titers following routine immunization, although it has not been studied.

In 2002, the FDA approved the combination vaccine Pediarix containing diphtheria, tetanus, acellular pertussis, hepatitis B and inactivated polio vaccines (5). This vaccine is currently recommended by the advisory committee for immunization practices (ACIP) for routine vaccination of infants at 2, 4, and 6 months. It can however, be given to healthy children <6 years of age. In an effort to limit the number of vaccines young survivors of pediatric cancer require, this vaccine will be incorporated into the revaccination schema of patients <6 years of age. In the last 5 years, several outbreaks of diseases which are vaccine preventable (varicella (6), pertussis (7), measles (8), mumps (9) have occurred in the United States in healthy individuals, emphasizing the risk of unprotected survivors of pediatric cancer and the need for evidence-based recommendations for their vaccination.

This trial will prospectively assess the immunogenicity and duration of response to routine childhood vaccines in pediatric survivors of cancer, including in age appropriate individuals, the recently approved vaccine, Tdap (BOOSTRIX) (10), whose use is substantiated by the recent increase in pertussis in the United States, the more immunogenic meningococcal vaccine, Menactra (11), and the recently approved quadrivalent human papilloma vaccine (12).

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a prospective, phase II study to determine the response (seroconversion or >3 fold rise in titer) of childhood survivors of cancer to routine childhood vaccines. The immune phenotype, function, and serum immunoglobulin levels of patients in CR 3-24 months following completion of chemotherapy will be assessed. Patients with a CD4 cell count >200/ul and an IgG level is > 500 mg/dl (>6 weeks after last dose of gamma globulin) will be vaccinated using schedules below. Vaccine titers will be obtained before and after vaccination at scheduled time points.

4.2 Intervention

Patients 3 -24 months following completion of cancer treatment who are in continued remission will be eligible for this trial. It is estimated that 150 pediatric patients complete chemotherapy each year at MSKCC and that approximately 75 patients will be enrolled on this study. Patients will be stratified based on age at diagnosis (<6 years or >6 years). After signing informed consent, detailed immunization history will be obtained and blood (10 ml) will be drawn to assess serum IgG subtypes, and IgM levels, T cell proliferation response to the mitogen, PHA (current standard of care) and lymphoid phenotype (CD4 and CD45RA subtype, CD8, CD19). Patients with a CD4 cell count >200/ul and a total IgG (IgG1-4) level >500 mg/dl will be vaccinated as detailed below. Patients with a CD4 cell count <200/ul and/or total IgG <500 mg/dl will be re-evaluated

every 2-3 months until these milestones are reached. Prior to vaccination, titers against tetanus, diphtheria, pertussis, polio, H flu, pneumococcus, Hepatitis B, measles, rubella, mumps, and varicella will be obtained.

Patients whose pre-vaccination titers are above the highest dilution run for a particular vaccine will receive only one booster vaccine, rather than a series of vaccines.

A. Immunization Schedule patients <7 years.

- Time 0 month: Administer Prevnar 13 #1, Hib #
- 1Time
- 1 months: Pediarix #1
- Time 2 months: Prevnar 13 #2, Hib #2
- Time 3-4 months: Administer Pediarix #2
- Time 4-6 months: Draw post vaccine titers

B. Immunization Schedule patients ≥7 years and <11 years of age:

- Time 0 months: Hib #1, Prevnar 13 #1, Hepatitis B #1
- Time 1 month:
  - TDAP (BOOSTRIX)
  - IPV #1(inactivated polio virus vaccine)
  - Hepatitis B #2
- Time 2-3 months: Prevnar 13 #2, Hib #2
- Time 3-6 months: Draw post vaccine titers. If <3 fold increase in tetanus titers give Td at 4-6 months.

C. Immunization Schedule patients ≥11 years of age

- Time 0 month: Hib#1, Prevnar 13 #1, Hepatitis B #1
- Time 1 month: Tdap (BOOSTRIX), Hepatitis B #2
- Time 2-3 months: Hib #2, Prevnar 13 #2, Menactra
- Time 3-6 months: IPV, Draw post vaccine titers
- Time 6-12 months: Gardasil (dose #2 given 2 months after first dose, and dose #3 given 6 months after first dose)

Regimens A, B, C

Time 4-12 months:

Administer Hepatitis #3 to patients not immunized prior to treatment for cancer, or with negative Hepatitis B titers after two immunizations.

Patients with response (defined in Section 12) to ≥ 3 vaccines measured at 3-6 months:

Measles, mumps, rubella (MMR) vaccine, measure response approximately 6-8 weeks later.

- Administer varicella vaccine, measure response approximately 6-8 weeks later.

Note: females of childbearing potential will have a pregnancy test prior to administration of any live vaccine

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Patients with negative titers at 3-6 months:

- (-) polio titers, immunize with inactivated poliovirus vaccine (Salk)
- (-) tetanus or pertussis titers, immunize with DTaP (<6 years of age) or TD (> 6 years of age)
- (-) pneumococcal or H flu titers, immunize with dose #3 Prevnar or Hib

Time 12-24 months: Females > 11 -26 years of age, without evidence of papilloma virus: Quadrivalent HPV (Types 6, 11, 16, 18) Recombinant Vaccine (Merck) at times 0, 2, and 6 months. Draw titers 6-8 weeks following last immunization.

5.0 THERAPEUTIC/DIAGNOSTIC AGENT

- **Pediarix (GlaxoSmithKline)**
  - Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (recombinant) and inactivated poliovirus Vaccine Combined
  - Must be <7 years of age
  - Dose: 0.5 ml intramuscularly

- **Diphtheria/tetanus +/- Acellular pertussis vaccine(s)**
  - < 7 years of age: DTaP, INFANRIX (GlaxoSmithKline)
    - Dose: 0.5 ml IM
  - ≥ 7 years: Tdap (BOOSTRIX, GlaxoSmithKline): tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed
    - Dose: 0.5 ml IM

- **IPOL®: inactivated polio virus, IPV**
  - Injection, suspension: Type 1 poliovirus 40 D antigen units/0.5 mL, Type 2 poliovirus 8 D antigen units/0.5 mL, and Type 3 poliovirus 32 D antigen units/0.5 mL (5 mL multidose vial) [may contain calf serum protein, neomycin, streptomycin, and polymyxin B]
    - Dose: 0.5 ml IM
    - May be administered with DTaP, Hib, HepB, varicella (chickenpox) vaccine, and measles-mumps-rubella vaccine.

- .**Haemophilus influenza b conjugate vaccine**

- PedVax HIB (PRP-OMP) (Merck)
  - 0.5 ml/dose intramuscularly OR

- HibTITER (Wyeth):
  - 0.5 ml intramuscularly

- **Recombinant Hepatitis B**
  - Engerix-B (GlaxoSmithKline)
    - 0-18 years: 10 mcg/0.5 ml, 0.5 ml intramuscularly at times 0,1, 6 months
    - >18 years: 20 mcg/ml, 1 ml intramuscularly at times 0,1,6 months OR

  - Recombivax (Merck)
    - 0-18 years of age: 5 mcg/0.5 ml, 0.5 ml intramuscularly at times 0,1, 6 months
    - >18 years: 10 mcg/ml, 1 ml intramuscularly at times 0,1,6 months

- **Protein conjugated pneumococcal vaccine, Prevnar** (Diphtheria CRM_{197} Protein; PCV7; Pneumococcal 13-Valent Conjugate Vaccine) (Wyeth)
  - Injection, suspension: 2 mcg of each saccharide for serotypes 1,3,5, 6A, 7F, 19A, 4, 9V, 14, 18C, 19F, and 23F, and 4 mcg of serotype 6B per 0.5 mL (0.5 mL) [contains 16 mcg total saccharide; also contains CRM_{197} carrier protein 20 mcg/0.5 mL and aluminum 0.125 mg/0.5 mL (as aluminum phosphate adjuvant)]
    - 0.5 ml intramuscularly
    - Storage Store refrigerated at 2°C to 8°C (36°F to 46°F).
    - May be administered simultaneously with DTaP, HbOC, IPV, hepatitis B vaccines, MMR, and varicella vaccine, when given in separate sites.

- **Protein conjugated meningococcal vaccine, Menactra II (Merck)**
  - solution: 4 mcg each of polysaccharide antigen groups A, C, Y and W-135 per 0.5 mL [conjugated to 48 mcg diphtheria toxoid protein; adjuvant and preservative free; vial stopper contains dry, natural latex rubber)
    - Dose 11 years to ≤55 years: 0.5 mL IM

- **Measles, mumps, rubella, MMR (Merck)**
  - Injection, powder for reconstitution: Measles virus 1000 $TCID_{50}$, rubella virus 1000 $TCID_{50}$, and mumps virus 20,000 $TCID_{50}$ [may contain neomycin 25 mcg, gelatin, human albumin, and bovine serum; produced in chick embryo cell culture]: 0.5 mL/dose
    - Dose: 0.5 ml subcutaneously

- **Live, attenuated varicella vaccine, Varivax (Merck)**
  - Varivax: Injection, powder for reconstitution [single-dose vial]: 1350 plaque-forming units (PFU) [may contain gelatin and trace amounts of neomycin]
    - Dose: 12 months to 12 years: 0.5ml subcutaneously
    - Dose: 13 years-adults: 0.5 ml subcutaneously, repeat 8 weeks later.

- **Quadrivalent HPV (Types 6, 11, 16, 18) Recombinant Vaccine (Merck)**

- Gardasil®: HPV 6 L1 protein 20 mcg, HPV 11 L1 protein 40 mcg, HPV 16 L1 protein 40 mcg, and HPV 18 L1 protein 20 mcg per 0.5 mL (0.5 mL) [contains polysorbate 80; prefilled syringe]
  - Dose: 0.5 ml given at 0 months, 2 months, and 6 months after dose 1

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Patient must be ≤18 years of age at cancer diagnosis

- Patient must be 3 to 24 months following completion of chemotherapy for malignant disease.
  a. For patients <12 months following completion of therapy, CR must be documented within 3 months of enrollment.
  b. For patients >12 months, CR must be documented at approximately 12 months and then only as clinically indicated

     i. For patients with leukemia: bone marrow aspirate defined as <5% blasts, absence of cytogenetic abnormality by FISH or karyotype (if applicable) and no evidence of CSF involvement (if applicable)
     ii. For patients with solid tumors remission will be determined by appropriate radiologic scans, and other tests, including bone marrow aspirate and biopsies demonstrating absence of extrinsic cells and absence of specific FISH or cytogenetic abnormality (if applicable),
     iii. For patients with lymphoma, remission will be determined by bone marrow aspirate and biopsy, radiologic scans and other tests. Bone marrow will show <5% blasts, absence of cytogenetic abnormality by FISH or karyotype (if applicable), and flow cytometry (if lymphoma specific marker present) and absence of CNS disease by spinal fluid (if applicable)

- Patient may be of either gender and of any ethnic background

- Patients or their guardians must be able to understand the nature and risk of the proposed study and be able to sign consent.

6.2 Subject Exclusion Criteria

- Karnofsky score <70%

- Patients who have received an autologous or allogeneic HCT

- Active uncontrolled bacterial or fungal infection

- Patients who have a history of previous allergic reaction to vaccinations currently recommended by the ACIP.

- Patients on any immunosuppressive drugs
- Patients who are being treated for an HIV associated malignancy
- Patients or guardians not signing informed consent.
- Patients with prior allergic reaction to any vaccine component or to latex
- Patients who have received Rituximab

7.0 RECRUITMENT PLAN

Each of the investigators on the protocol represent the DMT for children treated with cancer at MSKCC. Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study who then obtain consent. The Principal Investigator and co-PI through a limited waiver of authorization will review the patients medical records to ascertain the response to vaccinations and whether additional vaccines are required due to lack of response.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

8.0 PRETREATMENT EVALUATION

Unless otherwise stated, the following tests should be done within 30 days following enrollment.

- Physical examination and assessment of performance status (Appendix A)

- CBC
- Immune phenotype and PHA response (Appendix B)
- Serum total IgG and IgG subtypes 1-4, and IgM levels
- Vaccine titers against tetanus, diphtheria, pertussis, polio, H. Influenza, pneumococcus (12 serotypes), measles, mumps, rubella, varicella, hepatitis B, and meningococcus.
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9.0 TREATMENT/INTERVENTION PLAN

Patients who are in remission 3-24 months following completion of chemotherapy whose CD4 is >200/ul and total serum IgG level is ≥500 mg/dl will be vaccinated according to schedules below based on age.

Time interval between vaccines are approximate and may be delayed by 4 weeks as necessary. Delays of >4 weeks should be discussed with the PI or Co-PI and documented in the patients chart.

Patients may be vaccinated at MSKCC or by their local physicians. If vaccinated outside of Memorial Hospital, copies of the date, vaccine name, lot #, and site./route of injection should be sent to the PI or Co-PI

Regimen A. Immunization Schedule patients <7 years.

- Time 0 months: Prevnar 13 #1, Hib #1
- Time 1 months: Pediarix #1
- Time 2 months: Prevnar 13 #2, Hib #2
- Time 3-4 months: Pediarix #2
- Time 4-6 months: Draw post vaccine titers.
- Time 6-12 months: Administer Hepatitis #3 to patients not immunized prior to treatment for cancer, or with negative Hepatitis B titers after two immunizations.

Patients with response to at least 3 vaccines measured at 4-6 months:

- Measles, mumps, rubella (MMR) vaccine, measure response approximately 6-8 weeks later
- Administer varicella vaccine, measure response approximately 6-8 weeks later

Patients with negative titers at 4-6 months:

- (-) polio titers, immunize with inactivated poliovirus vaccine (Salk)
- (-) tetanus or pertussis titers, immunize with DTaP (<6 years of age) or TD (> 6 years of age)
- (-) pneumococcal or H flu titers, immunize with Prevnar #3 or Hib #3

Regimen B. Immunization Schedule patients ≥7 years and <11 years of age:

- Time 0 months: Hib #1, Prevnar13 #1, Hepatitis B #1
- Time 1 month: TDAP, IPV #1(inactivated polio virus vaccine), Hepatitis B #2
- Time 2-3 months: Prevnar 13 #2, Hib #2
- Time 3-6 months: Td #2, Draw post vaccine titers

- Time 6-12 months: Administer Hepatitis #3 to patients not immunized prior to treatment for cancer, or with negative Hepatitis B titers after two immunizations.

Patients with response to at least 3 vaccines measured at 3-6 months:

- Measles, mumps, rubella (MMR) vaccine, measure response approximately 6-8 weeks later
- If response to MMR, administer varicella vaccine, measure response approximately 6-8 weeks later

Patients with negative titers at 4-6 months:

- (-) polio titers, immunize with inactivated poliovirus vaccine (Salk)
- (-) tetanus or pertussis titers, immunize with DTaP (<6 years of age) or TD (> 6 years of age)
- (-) pneumococcal or H flu titers, immunize with Prevnar #3 or Hib#3

Regimen C. Immunization Schedule patients ≥11 years of age

- Time 0 month: Hib#1, Prevnar 13 #1, Hepatitis B #1
- Time 1 month: Tdap, Hepatitis B #2
- Time 2-3 months: Hib #2, Prevnar 13 #2, Menactra
- Time 3-6 months: IPV, Draw post vaccine titers
- Time 6-12 months: Gardasil (dose #2 given 2 months after first dose, and dose #3 given 6 months after first dose)

- Time 6-12 months: Administer Hepatitis #3 to patients not immunized prior to treatment for cancer, or with negative Hepatitis B titers after two immunizations.

Patients with response to at least 3 vaccines measured at 3-6 months:

- Measles, mumps, rubella (MMR) vaccine, measure response approximately 6-8 weeks later
- Varicella vaccine, measure response approximately 6-8 weeks later

Patients with negative titers at 4-6 months:

- (-) polio titers, immunize with inactivated poliovirus vaccine (Salk)
- (-) tetanus or pertussis titers, immunize with DTaP (<6 years of age) or TD (> 6 years of age)
- (-) pneumococcal or H flu titers, immunize with Prevnar #3 or Hib #3

Note: females of childbearing potential must have a pregnancy test (urine or blood) prior to administration of any live vaccine.

- Time 6-12 months: Females > 11 -26 years of age, without evidence of papilloma virus: Quadrivalent HPV (Types 6, 11, 16, 18) Recombinant Vaccine (Merck) at times 0, 2, and 6 months. Draw titers 6-8 weeks following last immunization.

10.0 EVALUATION DURING/AFTER TREATMENT/INTERVENTION

All patients will be monitored every 1-6 months for any adverse reactions to vaccines until vaccines are completed
Blood (15 cc) for titers to evaluate response to vaccinations at approximately 4-8 weeks following vaccination (if series after last dose in primary series), and at 12 -18 months .

11.0 TOXICITIES/SIDE EFFECTS

Diphtheria, tetanus, acellular pertussis

Likely

- Fever
- Redness, swelling, or soreness at the site of injection
- Tiredness or poor appetite

Less Likely

- Vomiting

Rare but serious

- Serious allergic reaction (less than one out of 1 million doses of DTaP)
- Guillain-Barré syndrome has occurred in a few people who have received the protein-conjugated meningococcal vaccine
- Seizure (jerking or staring) (about 1 child out of 14,000)
- Non-stop crying, for 3 hours or more (up to 1 child out of 1,000)
- Very high fever, over 105 degrees (about 1 child out of 16,000)
- Several other severe problems have been reported after DTaP vaccine. These include:
    - Long-term seizures, coma, or lowered consciousness, permanent brain damage.

Inactivated polio vaccine

Percentages noted with concomitant administration of DTP or DTaP vaccine and observed within 48 hours of injection.

Likely

- Fever ≥39°C (less than 38%)
- Irritability (7% to 65%), tiredness (4% to 61%), Anorexia (1% to 17%)
- Local: Injection Site: Tenderness (≤29%), pain (13%), swelling (≤11%)

Less likely

- Vomiting (1% to 3%)
- Local: Injection site Erythema (≤3%) induration (1%)
- Persistent crying (up to 1% reported within 72 hours)

Rare but serious

- Post marketing and/or case reports: Guillain-Barré syndrome has been temporally related to another inactivated poliovirus vaccine.
- Serious allergic reaction including difficulty breathing, hoarseness or wheezing, hives, paleness, weakness, a fast heart beat, or dizziness within a few minutes to a few hours after the shot.

Haemophilus influenza b conjugate vaccine

Likely

- Redness, warmth, or swelling at the injection site (up to 1/4 of children)
- Fever over 101°F (up to 1 out of 20 children)

Rare but serious

- Serious allergic reaction including difficulty breathing, hoarseness or wheezing, hives, paleness, weakness, a fast heart beat, or dizziness within a few minutes to a few hours after the shot.

Protein conjugated pneumococcal vaccine, Prevnar 13

Likely

- Redness, swelling at the site of injection
- Fever
- Fussiness
- Loss of appetite

Rare, but serious

- Serious allergic reaction including difficulty breathing, hoarseness or wheezing, hives, paleness, weakness, a fast heart beat, or dizziness within a few minutes to a few hours after the shot.

Recombinant Hepatitis B

Likely

- soreness at injection site, lasting a day or two (up to 1 out of 11 children and adolescents, and about 1 out of 4 adults)
- mild to moderate fever (up to 1 out of 14 children and adolescents and 1 out of 100 adults)

Rare but serious

• serious allergic reaction (very rare) reactions are extremely rare with any vaccine, including difficulty breathing, hoarseness or wheezing, hives, paleness, weakness, a fast heart beat or dizziness.

Measles, mumps, rubella, MMR (Merck)

Likely

- Fever (up to 1 person out of 6)
- Mild rash (about 1 person out of 20)
- Temporary pain and stiffness in the joints, mostly in teenage or adult women (up to 1 out of 4)

Less likely

- Swollen lymph nodes in the neck or cheeks

Rare, but serious

- Seizure (jerking or staring) caused by fever (about 1 out of 3,000 doses)
- Temporary low platelet count, which can cause a bleeding disorder (about 1 out of 30,000 doses)
- Serious allergic reaction (less than 1 out of a million doses)
- Deafness
- Long-term seizures, coma, or lowered consciousness
- Permanent brain damage

Live attenuated varicella vaccine, Varivax

Likely

- Soreness or swelling where the shot was given (about 1 out of 5 children and up to 1 out of 3 adolescents and adults)
- Fever (1 person out of 10, or less)
- Mild rash, up to a month after vaccination (1 person out of 20, or less). It is possible for these people to infect other members of their household, but this is *extremely* rare.

Rare, but serious

- Pneumonia (very rare)

- Other serious problems, including severe brain reactions and low blood count
- Seizure (jerking or staring) (about 1 child out of 14,000)
- Serious allergic reaction including difficulty breathing, hoarseness or wheezing, hives, paleness, weakness, a fast heart beat, or dizziness within a few minutes to a
- few hours after the shot.

Conjugated Meningococcal vaccine, Menactra

Likely

Redness or soreness at the injection site

Less likely:

- Fever

Rare, but serious

- Serious allergic reactions, within a few minutes to a few hours of the shot
- Guillain-Barré Syndrome (very rare)

Gardasil®, human papilloma virus vaccine

Likely

- Pain at the injection site (about 8 people in 10)
- Redness or swelling at the injection site (about 1 person in 4)
- Mild fever (100°F) (about 1 person in 10)
- Itching at the injection site (about 1 person in 30)
- Moderate fever (102°F) (about 1 person in 65)

Rare, but serious

- Life-threatening allergic reactions from vaccines are very rare. If they do occur, it would be within a few minutes to a few hours after the vaccination.
- Pneumonia (very rare)
- Other serious problems, including severe brain reactions and low blood count
- Seizure (jerking or staring) caused by fever (less than 1 person out of 1,000).

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Vaccine response will be determined for each vaccine administered.

For diphtheria, tetanus, polio, H flu, measles, mumps, rubella, varicella, response will be defined as seroconversion in a seronegative patient or a 3-fold greater increase in titer following immunization.

For pneumococcus, response will be either seroconversion in a seronegative patient or a >3 fold rise in titer against serotypes 14, 19, and 23 contained in Prevnar 13.

Partial response will be defined as 1.5-2 fold increase over baseline titers, or response to some but not all measured serotypes contained in the vaccine (pneumococcus or polio virus)

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at anytime the patient relapses with their cancer he/she will be taken off study.

If at anytime the patient develops unacceptable toxicity, including an allergic reaction to a vaccine component, he/she will be removed from study.

If at anytime the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

If at any time the patient is unwilling to continue scheduled vaccinations, he/she will be removed from study.

If at any time, the primary oncologist or study doctor believes it is in the best interest of the patient to be withdrawn from the study, the patient will be removed from the study withdrawn.

14.0 BIOSTATISTICS

A single arm phase 2 design is used to estimate the response rates of childhood survivors of cancers to routine childhood vaccines. The definition of response for each vaccine, based on the increase in titer measures after vaccination, is provided in Section 12.

The literature on vaccine response after childhood cancer is sparse, with reports based on studies with small patient numbers. As a result, the primary objective of this study is to derive precise estimates of response for vaccines. Seventy five patients will be enrolled in this study enabling the true response rate per vaccine to be estimated within +/- 0.11. It is unclear whether age is associated with vaccine response. To insure a balance between younger and older children in this study, patient accrual will be stratified by age (< 6 vs > 6).

To assess a specific vaccine response rate, a one stage exact binomial test will be applied. A vaccine will be considered insufficiently active if the probability of response in the population is less than 0.70. For each vaccine, if at least 61 responses are observed among the 75 patients under study, we will conclude that the vaccine is sufficiently active. This design has power greater than 0.90 per vaccine if the probability of response is 0.88 using a one-sided 0.01 size test. The significance level 0.01 was chosen to account for the multiplicity of vaccines tested within each re-immunization schedule. It is anticipated that accrual will be completed within 2 years.

A secondary aim of the study is to assess the association between vaccine response and immunologic reconstitution factors. The generalized estimating equation (Liang and Zeger 1986) approach will be used to model the relationship between the immunologic reconstitution factors and vaccine response. The marginal regression model used for this relationship is written as

$$\log[p_{ijt} / (1-p_{ijt})] = \alpha + x_{it}\beta$$

where p_{ijt} is the probability that a response to vaccine *j* occurs for patient *i* at time *t*, and x_{it} is the vector of immunologic reconstitution measures for patient *i* at time *t*. Each component in the marginal regression coefficient vector, measures the change in the logit of the probability of a

response for a unit change in the corresponding immunologic reconstitution measure (ie. CD4 cell count, PHA response, naive CD4+ CD45RA+, or memory CD20+CD27+IgD negative). Potential confounding factors for this analysis include vaccination schedule, age at cancer diagnosis and completion of therapy, type of cancer and administered chemotherapy.

The duration of response will be estimated using the cumulative incidence function. A competing risk regression model will be used to determine the factors associated with the duration of response. Toxicities will be recorded and summarized at the conclusion of the study.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligiblity as defined in the section entitled Criteria for Patient/Subject Eligiblity.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligiblity Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the written consent/verbal script and a completed Eligiblity Checklist must be faxed to PPR.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The RSA will assist the PI and co-PI whose responsibilities will include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.
The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Quality AssuranceThe Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials'

which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

During the protocol development and review process, each protocol will be assessed for it's level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for it's level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation

17.0 PROTECTION OF HUMAN SUBJECTS

Patients or their guardians will be informed of the progress of the research study, and of any new findings, which might affect their willingness to participate. Parents will be given vaccination information sheets (VIS, appendix C) on all vaccines administered. These sheets include numbers to call for any adverse event or questions regarding vaccines.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use

and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org containing the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form.
  - The PI's signature and the date it was signed are required on the completed report.

If any significant side effects potentially attributable to a vaccine occur, a Vaccine Adverse Event Reporting System (VAERS) form will be filed using the VAERS web site at www.vaers.org

18.0 INFORMED CONSENT PROCEDURES

Patients recruited to this study are individuals referred by their primary oncologist for revaccination will be recruited to this protocol. Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. Guardians of the patients or the patient if older than 18 years of age will provide written informed consent and a copy of this wil be includec in the patient's chart and given to the patient or guardian. All research protocols and consent forms are reviewed by the IRB. The consent form meets the

requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information.

In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must must receive a copy of the signed informed consent form.

19.0 REFERENCE(S)

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20.0 APPENDICES

Appendix A. Karnofsky and Performance Status
Appendix B. Phenotype and function panel
Appendix C. Vaccine Information Sheets (VIS)