A POST MARKETING EVALUATION OF THE SAFETY OF FLUMIST IN CHILDREN 24-59 MONTHS OF AGE IN A MANAGED CARE SETTING

Study Agent: Refrigerated FluMist

MedImmune Protocol Number: MI-MA162

IND Number: BB-IND 9204

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Principal Investigator Agreement:
I, the undersigned, have reviewed this protocol and I agree to conduct this protocol in accordance with Good Clinical Practice and with the U.S. Code of Federal Regulations governing Institutional Review Boards (21 CFR 56) and the obligations of clinical investigators (21 CFR 312).

Signature_____ Date_____
Printed Name_____

LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
att	attenuated
ca	cold-adapted
CFR	Code of Federal Regulations
CI	confidence interval
FDA	US Food and Drug Administration
HMO	health maintenance organization
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
KITS	Kaiser Immunization Tracking System
MAE	medically attended event
RAD	reactive airways disease
RD	risk difference
RR	relative risk
SAE	serious adverse event
TIV	trivalent inactivated influenza vaccine
ts	temperature sensitive
US	United States

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STUDY ABSTRACT

TITLE:

A Post Marketing Evaluation of the Safety of FluMist in Children 24-59 Months of Age in a Managed Care Setting

RATIONALE:

In September 2007, FluMist received marketing approval by the US FDA to expand the indication for active immunization for the prevention of disease caused by influenza A and B viruses to children 24 to 59 months of age. As part of a post-marketing commitment between MedImmune and the FDA to further describe the safety profile of FluMist in children <5 years of age, the currently proposed study will identify from database review approximately 25,000 children aged 24 to 59 months who have received FluMist. Identification of 25,000 unique vaccinees (i.e., 25,000 FluMist recipients vaccinated in one or more seasons) is expected to take multiple seasons. Thus, the multi-year design will also permit a safety assessment of annual revaccination in children who receive FluMist in 2 or more consecutive years.

OBJECTIVES:

The objectives of this study are:

1) To assess the safety of FluMist vaccination
   - Rates of medically attended events (MAEs; as defined in Section 4.1) in FluMist recipients, including serious adverse events (SAEs), anaphylaxis (see Appendix A), urticaria, asthma, wheezing, pre-specified grouped diagnoses (see Appendix B), and rare events potentially related to wild-type influenza (see Appendix C), will be compared to rates in multiple non-randomized control groups.

2) To assess the safety of annual FluMist re-vaccination
   - Rates of MAEs in the subset of children who receive FluMist in ≥2 consecutive years will be compared to rates in first-time vaccinees during the same season.

3) To assess the safety of FluMist vaccination in children previously vaccinated with trivalent inactivated influenza vaccine (TIV)
   - Rates of MAEs in the subset of children who received one or more prior TIV vaccinations will be compared to rates in children who did not receive prior TIV.

DESIGN:

This is an observational study conducted over multiple years with multiple non-randomized control groups. Children will be screened for vaccination and immunized with FluMist as part of routine clinical practice within the Kaiser Permanente Health Care Plan. The study will extract database information for children who receive one or two vaccinations (depending on prior vaccination status) with FluMist. Children not previously vaccinated against influenza are recommended to receive two doses of vaccine approximately 1 month apart, while children who

have been previously vaccinated against influenza are recommended to receive a single dose of vaccine.

The study is expected to begin in the Fall of 2007 and continue until approximately 25,000 unique FluMist recipients are vaccinated and follow-up has been completed for at least 6 months after the final dose has been administered to the final recipient. The study population will include at least 8,000 children who are 24-35 months of age at the time of initial vaccination with FluMist. The goal is to complete enrollment of 25,000 children by December 2012.

PATIENT POPULATION:

Members of the Kaiser Permanente Health Care Plan may be included in this study as part of routine care at their participating health centers within the Kaiser Permanente health maintenance organization (HMO) of Northern California.

Kaiser Permanente Health Care Plan members who received FluMist at participating health centers will be identified in the Kaiser Immunization Tracking System (KITS) database. Study outcomes will be assessed for FluMist vaccinees 24 to 59 months of age.

Three non-randomized control groups will be used for MAE and SAE comparisons:

- FluMist recipients will serve as their own controls using a defined reference period.
- Kaiser Permanente Health Care Plan members who did not receive influenza vaccine for the season (either FluMist or TIV) will be identified and matched to FluMist recipients.
- Kaiser Permanente Health Care Plan members who received the current TIV formulation for the season, but not FluMist, at a Kaiser HMO during the same month that the reference FluMist recipient was vaccinated will be identified.

TREATMENT:

Identified recipients will have received one or two vaccinations with FluMist or TIV, depending on prior vaccination status. Children not previously vaccinated against influenza are recommended to receive two doses of vaccine approximately 1 month apart, while children who have been previously vaccinated against influenza are recommended to receive a single dose of vaccine.

ASSESSMENT OF ENDPOINTS:

Analyses will be performed by period (1, 3, 21, or 42 days post dose; 6 months post dose; entire study period), setting (clinic, hospital, emergency department, all settings), and dose number (one or two [when feasible]). Event rates will be presented per 1000 person-months. Crude relative risks and corresponding exact 95% CIs will be constructed for each event and will constitute the primary analysis. For the final report, safety comparisons will also be performed using the Cox proportional hazards model implementing the counting–process style of input. Statistically significant increased risk associated with FluMist vaccination will be demonstrated if the lower bound of the exact 95% CI is >1.000. Likewise, statistically significant decreased risk associated with FluMist vaccination will be demonstrated if the upper bound of the exact 95% CI is <1.000. Statistical significance will be determined prior to rounding.

Individuals who receive two or more consecutive annual vaccinations with FluMist will be identified in the KITS database. For these individuals, rates of SAEs and other MAE endpoints will be analyzed by consecutive revaccination year (i.e., second annual revaccination, third annual revaccination) and compared to rates in first-time vaccinees during the same season. The safety of FluMist vaccination in children previously vaccinated with TIV will be assessed by comparing event rates among such children to rates in FluMist recipients not previously vaccinated with TIV.

1 INTRODUCTION

1.1 Background

Influenza is the leading cause of vaccine-preventable morbidity and mortality in the United States (US). Influenza epidemics occur nearly every year and are responsible for an average of approximately 36,000 deaths per year in the US (Thompson 2003). While influenza causes illness in all age groups, rates of infection are highest among children, and otherwise healthy children were recently recognized to be at increased risk for influenza-related hospitalization (Bridges 2003). Among young children, hospitalization rates due to influenza are reported to be comparable to rates in the elderly (Izurieta 2000, Neuzil 2000, Poehling 2006). The majority of influenza-related deaths in children occur in those <5 years of age, and nearly half of the pediatric influenza-related deaths are in children who are otherwise considered healthy (Bhat 2005). Influenza infection is also responsible for excess rates of outpatient clinic visits and emergency room visits in children <5 years of age (Poehling 2006). In addition to the morbidity and mortality in children themselves as a result of influenza infection, children are also the major pathway by which influenza infection is spread within the community (Fox 1982, Neuzil 2002, Weycker 2005).

Vaccination is the primary method for preventing illness and severe complications related to influenza. Annual vaccination is recommended for any person 6 months of age or older who is at increased risk for complications of influenza and for those in close contact with persons at high risk. In 2004 the Advisory Committee on Immunization Practices (ACIP) recommended influenza vaccination of all children 6-23 months of age, as well as their out-of-home caregivers and household contacts (CDC 2004). In February 2006, ACIP updated these recommendations to include children up to 59 months of age and their caregivers and contacts (CDC 2006). Prevention of spread of influenza by vaccination of children is an important part of influenza control.

1.2 Description of FluMist

FluMist® (Influenza Virus Vaccine Live, Intranasal) is a live, attenuated trivalent nasally administered vaccine originally licensed in the United States in 2003 for the prevention of disease caused by influenza A and B viruses contained in the vaccine in healthy children and adolescents 5-17 years of age and healthy adults 18-49 years of age. In September 2007, FluMist received marketing approval by the US FDA to expand the indication for active immunization for the prevention of disease caused by influenza A and B viruses to children 24 to 59 months of age.

The active agents of FluMist consist of two cold-adapted (*ca*), temperature sensitive (*ts*), attenuated (*att*) influenza strains of type A (i.e., A/H1N1 and A/H3N2), and one *ca*/*ts*/*att* influenza strain of type B. The type A and B strains were adapted to grow in primary chick kidney cells at 25°C by sequential passage at progressively lower temperatures. During the process of cold adaptation, each virus acquired mutations that conferred unique biological phenotypes of cold adaptation, temperature sensitivity, and attenuation, which distinguish these viruses from wild-type influenza viruses.

1.3 Rationale for Study

As part of a post-marketing commitment between MedImmune and the FDA to further describe the safety profile of FluMist in children <5 years of age, the currently proposed study will identify from database review approximately 25,000 children aged 24 to 59 months who have received FluMist. Identification of 25,000 unique vaccinees (i.e., 25,000 FluMist recipients vaccinated in one or more seasons) is expected to take multiple seasons. Thus, the multi-year design will also permit a safety assessment of annual revaccination in children who receive FluMist in 2 or more consecutive years.

2 STUDY OBJECTIVES AND OVERVIEW

2.1 Objectives

The objectives of this study are:

1. To assess the safety of FluMist vaccination
   - Rates of medically attended events (MAEs; as defined in Section 4.1) in FluMist recipients, including serious adverse events (SAEs), anaphylaxis (see Appendix A), urticaria, asthma, wheezing, pre-specified grouped diagnoses (see Appendix B), and rare events potentially related to wild-type influenza (see Appendix C), will be compared to rates in multiple non-randomized control groups.

2. To assess the safety of annual FluMist re-vaccination
   - Rates of MAEs in the subset of children who receive FluMist in ≥2 consecutive years will be compared to rates in first-time vaccinees during the same season.

3. To assess the safety of FluMist vaccination in children previously vaccinated with trivalent inactivated influenza vaccine (TIV)
   - Rates of MAEs in the subset of children who received one or more prior TIV vaccinations will be compared to rates in children who did not receive prior TIV.

2.2 Overview

This is an observational study conducted over multiple years with multiple non-randomized control groups. Children will be screened for vaccination and immunized with FluMist as part of routine clinical practice within the Kaiser Permanente Health Care Plan. The study will extract database information for children who receive one or two vaccinations (depending on prior vaccination status) with FluMist. Children not previously vaccinated against influenza are recommended to receive two doses of vaccine approximately 1 month apart, while children who have been previously vaccinated against influenza are recommended to receive a single dose of vaccine.

The study is expected to begin in the Fall of 2007 and continue until approximately 25,000 unique FluMist recipients are vaccinated and follow-up has been completed for at least 6 months after the final dose has been administered to the final recipient. The study population

will include at least 8,000 children who are 24-35 months of age at the time of initial vaccination with FluMist. The goal is to complete enrollment of 25,000 children by December 2012.

Because the study will extract database information over multiple years, information from the same child may be extracted over subsequent years.

3 STUDY PROCEDURES

3.1 Patient Population

Members of the Kaiser Permanente Health Care Plan may be included in this study as part of routine care at their participating health centers within the Kaiser Permanente health maintenance organization (HMO) of Northern California.

3.1.1 FluMist Recipients

Kaiser Permanente Health Care Plan members who received FluMist at participating health centers will be identified in the Kaiser Immunization Tracking System (KITS) database.

Study outcomes will be assessed for FluMist vaccinees 24 to 59 months of age, per the newly approved indication and product label. FluMist recipients will be identified via automated extraction of data from the KITS database. FluMist recipients with underlying high-risk medical conditions will be identified via automated extraction of data and excluded from the primary analysis. Such extraction may not allow complete identification of individuals who received FluMist outside of the indication.

3.1.2 Control Groups

Three non-randomized control groups will be used for MAE and SAE comparisons.

Within-Cohort FluMist Recipients

FluMist recipients will serve as their own controls using a defined reference period.

Matched Concurrent Unvaccinated Controls

Kaiser Permanente Health Care Plan members who did not receive influenza vaccine for the season (either FluMist or TIV) will be identified and matched to FluMist recipients. Matching will be based on the following factors:

- Age: born in the same calendar quarter as the reference FluMist vaccinee.
- Medical center: same as the reference FluMist vaccinee.

Factors such as gender, health care utilization level, prior influenza vaccination history (if feasible), and vaccine compliance (if feasible) will be handled as covariates in the proposed Cox proportional hazards model. Health care utilization level will be defined for FluMist vaccinees and controls as "high" (≥2 visits to a Kaiser HMO within the 6 months prior to the date of vaccination of the reference FluMist vaccinee) or "low" (≤1 visit).

Children who have evidence of medical conditions that put them at high risk for complications of influenza (e.g., chronic cardiovascular and pulmonary disease) will be excluded from this control group. The process for identifying controls may not successfully exclude all controls with underlying high-risk medical conditions specified in the recommendations for TIV.

Matched Concurrent TIV Recipient Controls

Kaiser Permanente Health Care Plan members who received the current TIV formulation but not FluMist for the season at a Kaiser HMO during the same month that the reference FluMist recipient was vaccinated will be identified. Matching will also be based on the following factors:

- Age: born within the same calendar quarter as the reference FluMist vaccinee.
- Medical center: same as the reference FluMist vaccinee.

Factors such as gender, health care utilization level, prior influenza vaccination history (if feasible), and vaccine compliance (if feasible) will be handled as covariates in the proposed Cox proportional hazards model. Health care utilization level will be defined for FluMist vaccinees and controls as "high" or "low" as previously described.

Study Day 0 for TIV controls is defined for each control as the date of the first dose of TIV for the season. Subsequent study days are numbered sequentially thereafter.

Children who have evidence of medical conditions that put them at high risk for complications of influenza (e.g., chronic cardiovascular and pulmonary disease) will be excluded from this control group. The process for identifying controls may not successfully exclude all controls with underlying high-risk medical conditions specified in the recommendations for TIV.

3.2 Participant Identification Procedures

Individuals vaccinated with FluMist will be identified for inclusion in this study via the KITS database. Immunizations of Kaiser Permanente members are recorded in this database as part of routine care. Because each recipient has a unique medical record number assigned once enrolled in the Kaiser Permanente Health Care Plan and because administration records of all vaccinees are entered in the KITS database, the study population can be assembled from the KITS system on an ongoing basis. The lot number of administered vaccine is entered in the KITS immunization database for each vaccinee.

3.3 Vaccines

3.3.1 Vaccine Supplies and Accountability

FluMist will be commercially obtained by Kaiser Permanente and provided to participating health care centers in the Kaiser Permanente Health Care Plan in Northern California for each influenza season.

3.3.2 Treatment Regimens

Identified recipients will have received one or two vaccinations with FluMist or TIV, depending on prior vaccination status. Children not previously vaccinated against influenza are

recommended to receive two doses of vaccine approximately 1 month apart, while children who have been previously vaccinated against influenza are recommended to receive a single dose of vaccine.

4 SAFETY ASSESSMENT

Safety outcome ascertainment will primarily be achieved by passive methods conducted via extraction of data from the KITS database.

4.1 Adverse Events: Medically Attended Events

Safety evaluation will include assessments of MAEs (including SAEs; Section 4.2), assessed using medical diagnostic codes and recorded in the KITS database.

For the purpose of this study, an MAE is defined as a coded medical diagnosis made by a health care provider and associated with a medical encounter for a health plan member in one of three distinct settings: out-patient medical clinic, emergency department, or a hospital admission. One or more MAEs could be assigned for a single encounter.

MAEs, including MAEs of asthma and wheezing, will be identified for an individual vaccine recipient through 42 days after each vaccination via automated database extraction. MAEs of asthma for children without a prior diagnosis of asthma will be identified through the entire study period.

4.2 Serious Adverse Events

4.2.1 Definition of Serious Adverse Events

A Serious Adverse Event (SAE) is any adverse event that results in any of the following outcomes:

- Death
- Life-threatening*
- Inpatient hospitalization or prolongation of existing hospitalization‡
- Persistent or significant disability or incapacity†
- Congenital anomaly/birth defect (in the offspring of a subject)
- An important medical event that may not result in death, threaten life or require hospitalization may be considered a serious adverse event when, **based upon appropriate medical judgment**, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

*Life threatening: An adverse event is life threatening if the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

‡Hospitalization: An inpatient hospitalization will be defined as an admission (or emergency room visit) for a period greater than 24 hours. Hospitalization for either elective surgery related to a pre-existing condition which did not increase in severity or frequency following initiation of the study or for routine clinical procedures¶ (including hospitalization for "social" reasons) that are not the result of an adverse event need not be considered as adverse events and are therefore not serious adverse events.

¶Routine Clinical Procedure: A procedure which may take place during the study period and should not interfere with the study product administration or any of the ongoing protocol specific procedures. If anything untoward is reported during an elective procedure, that occurrence must be reported as an adverse event or serious adverse event, according to the usual criteria.

†Disabling/incapacitating: An adverse event is incapacitating or disabling if the event results in a substantial disruption of the subject's ability to carry out normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle).

SAEs will be identified by investigator review of MAE line listings every 4-6 weeks during the vaccination period, and relationship to vaccine will be assessed (see Section 4.3). SAEs will be identified for an individual vaccine recipient through 42 days after each vaccination.

After completion of the vaccination period, SAEs in the hospitalization setting and SAEs leading to death will be identified by investigator review of line listings every 2 months and relationship to vaccine will be assessed (see Section 4.3). Hospitalizations and deaths will be identified for an individual vaccine recipient through 6 months after each vaccination.

4.2.2 Notification of Sponsor of Serious Adverse Events

For SAEs that Occur within 42 Days after Vaccination

Within 24 hours of identifying a serious adverse event (by review of database extractions) ***regardless of causality assessment,*** the investigator must complete the SERIOUS ADVERSE EVENT (SAE) REPORT FORM and fax it to MedImmune Product Safety.

For SAEs that Occur >42 Days after Vaccination

Within 24 hours of identifying a serious adverse event (by review of database extractions) assessed by the investigator as *possibly, probably, or definitely related to study vaccine,* the investigator must complete the SERIOUS ADVERSE EVENT (SAE) REPORT FORM and fax it to MedImmune Product Safety.

Note for all SAEs regardless of temporal relationship to vaccination: Provide all available information at time of form completion. When additional information becomes available, submit a follow-up Serious Adverse Event (SAE) Report Form with the new information.

MedImmune contact information:

Product Safety
MedImmune
One MedImmune Way
Gaithersburg, MD 20878
Fax: 301-398-4205

MedImmune, as sponsor of the study being conducted under an Investigational New Drug Application (IND), is responsible for reporting certain serious adverse events as IND safety reports to the FDA, other applicable regulatory authorities, and participating investigators, in accordance with the U.S. Code of Federal Regulations (21 CFR 312.32 and 312.33) ICH Guidelines, and/or local regulatory requirements. The sponsor may be required to report certain serious adverse events to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by the sponsor as soon as it becomes available.

4.3 Assessment of Relationship

The investigator is required to provide an assessment of relationship of serious adverse events to the study product. A number of factors should be considered in making this assessment including: 1) the temporal relationship of the event to the administration of study product; 2) whether an alternative etiology has been identified; and 3) biological plausibility. The following guidelines should be used by investigators to assess the relationship of an SAE to study product administration.

Relationship assessments that indicate an **"Unlikely Relationship"** to study product:

None: The event is related to an etiology other than the study product (the alternative etiology must be documented in the study subject's medical record).

Remote: The event is unlikely to be related to the study product and likely to be related to factors other than study product.

Relationship assessments that indicate a **"Likely Relationship"** to study product:

Possible: There is an association between the event and the administration of the study product and there is a plausible mechanism for the event to be related to study product; but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.

Probable: There is an association between the event and the administration of study product, a plausible mechanism for the event to be related to the study product and the event could not be reasonably explained by known characteristics of the subject's clinical status or an alternative etiology is not apparent.

Definite: There is an association between the event and the administration of study product, a plausible mechanism for the event to be related to the study product and causes other than the study product have been ruled out and/or the event re-appeared on re-exposure to the study product.

4.4 Safety Management During the Study

The investigator has primary responsibility for the ongoing review of safety data throughout the study. This includes review of line listings as previously described in Sections 4.1 and 4.2.1. The MedImmune Product Safety Specialist has responsibility for the receipt and review of SAEs reported by the investigator.

5 STATISTICAL CONSIDERATIONS

5.1 General Considerations

Categorical baseline data will be summarized by the enumeration of children displaying distinctive characteristics and its percentage. Continuous baseline measures will be summarized by descriptive statistics such as mean, median, standard deviation, and range.

The age, gender, medical center, prior year health care utilization level, prior influenza vaccination status (if feasible), and vaccine compliance (if feasible) of the experimental and control groups will be summarized by group for descriptive purposes. Race information is not available in the Kaiser HMO databases.

Rates of events will be presented per 1000 person-months or similar scale.

Crude relative risks and corresponding exact 95% confidence intervals (95% CIs) will be constructed for each event and will constitute the primary analysis. For anticipated serious rare events, effect sizes will be presented as risk differences (expressed as events per 10,000 children vaccinated) as well as hazard ratios (relative risks).

For the final report, safety comparisons will also be performed using the Cox proportional hazards model implementing the counting–process style of input (Andersen and Gill 1982) or a similar method. This style of input facilitates the use of time-dependent covariates and calendar time as the time structure of the model. The relative risk for the main effect (or a covariate) will be estimated by e^{β}, where β is the regression coefficient for the specific effect or covariate of interest. Ninety-five percent CIs for the relative risk will be calculated using a normal approximation, with the variance derived from the appropriate diagonal element of the estimated covariance matrix. In circumstances where the number of events is insufficient to allow the Cox model to converge, outcomes will be appropriately summarized by a less-adjusted statistical method, by crude relative risk, or provided in list format. Initial analyses will model the first

incidence of each event or class of event (e.g., respiratory events) as the response variable. All of the events ascertained in this study are medically attended and it is expected that, among the events of chief interest, most participants will experience zero or one visit during the period of observation. Based upon post hoc review, if an event or class of events occurs more than once within each of a significant number of participants, analyses that incorporate multiple events per participant may be conducted. Multiple-event analyses will include a robust sandwich estimate of variance. Exploratory analyses may be performed using this approach.

A statistically significant increased risk associated with FluMist vaccination will be declared if the lower bound of the two-sided 95% CI is greater than 1. Due to the exploratory nature of the study and the lack of formal hypothesis testing, multiple CIs will be constructed without multiplicity adjustment. Due to the large number of unadjusted CIs to be evaluated, it is expected that a number of CIs will not include 1 and suggest higher event rates in the FluMist group due to chance alone. Therefore, further statistical and medical assessments may be performed for events with observed increases that are statistically significant and/or medically important.

5.2 Sample Size

Post-marketing safety studies are by nature hypothesis generating and typically include multiple statistical comparisons. Therefore, rather than equivalence hypotheses, difference hypotheses are appropriate for power and sample size calculations.

Identification of at least 25,000 children 24-59 months of age in each arm of the study (FluMist recipients, TIV recipient controls, and unvaccinated controls) will provide at least 80% power to detect a statistically significant increase in relative risk for MAEs that occur at a rate of 1 in 1000 if the true relative risk for FluMist ≥2.

The proportion of persons experiencing a new diagnosis of asthma during the influenza vaccination season is estimated to be between 1% (1 in 100) and 2% (1 in 50). For events that occur at rates of 1 in 100 or 1 in 50, the study provides ≥80% power to observe a statistically significant increased relative risk if the true relative risk is ≥1.27 or ≥1.19, respectively.

5.3 Patient Populations

The populations to be assessed are FluMist recipients, TIV recipient controls, and unvaccinated controls (see Section 3.1).

5.4 Endpoints

A summary of the planned analyses is presented in Table 1. Analyses will be performed by period (1, 3, 21, or 42 days post dose; 6 months post dose; entire study period), setting (clinic, hospital, emergency department, all settings), and dose number (one or two [when feasible]). Event rates will be presented per 1000 person-months. Crude relative risks and corresponding exact 95% CIs will be constructed for each event. Statistically significant increased risk associated with FluMist vaccination will be demonstrated if the lower bound of the exact 95% CI is >1.000. Likewise, statistically significant decreased risk associated with FluMist vaccination

will be demonstrated if the upper bound of the exact 95% CI is <1.000. Statistical significance will be determined prior to rounding.

Table 1 Summary of Planned Analyses

Events	Periods	Non-Randomized Controls		
		Within-Cohort	Matched Concurrent	
			Unvaccinated	TIV
MAEs of anaphylaxis (see Appendix A) and urticaria	1 day and 3 days	Rates, RR, and RD	Rates, RR, and RD	Rates, RR, and RD
MAEs of asthma and wheezing	21 days	Rates, RR, and RD	Rates, RR, and RD	Rates, RR, and RD
	42 days	Proportional Hazards model adjusted for seasonality	Rates, RR, and RD	Rates, RR, and RD
MAEs within the pre-specified grouped diagnoses (see Appendix B)	21 days and 42 days	Rates, RR, and RD	Rates, RR, and RD	Rates, RR, and RD
MAEs that are rare events potentially related to wild-type influenza (see Appendix C)	21 days and 42 days	Rates, RR, and RD	Rates, RR, and RD	Rates, RR, and RD
All MAEs meeting the criteria of an SAE	21 days and 42 days	Rates, RR, and RD	Rates, RR, and RD	Rates, RR, and RD
All MAEs in the emergency department setting	21 days and 42 days	Rates, RR, and RD	Rates, RR, and RD	Rates, RR, and RD
All MAEs in the hospitalization setting	21 days and 42 days	Rates, RR, and RD	Rates, RR, and RD	Rates, RR, and RD
	6 months	--	Rates, RR, and RD	Rates, RR, and RD
All MAEs for deaths	6 months	--	Rates, RR, and RD	Rates, RR, and RD
MAEs that are rare events potentially related to wild-type influenza that also occur in the hospitalization setting or result in death	6 months	--	Rates, RR, and RD	Rates, RR, and RD
	Entire study period[a]	--	Rates, RR, and RD	Rates, RR, and RD
MAEs of asthma in children without a prior diagnosis of asthma	Entire study period[a]	--	Rates, RR, and RD	Rates, RR, and RD

RD = risk difference; RR = relative risk

Analyses will be performed by setting (all settings, clinic, hospital, emergency department) and dose number (Dose One, Dose Two) with the following exception: post Dose Two analyses for matched TIV controls may not be feasible.

a. The end of the "entire study period" is defined as 6 months after completion of the primary dosing regimen of the last identified vaccinated recipient.

Vaccinees will be followed for Days 0 to 42 post-vaccination for all MAEs (including SAEs and pre-specified groups diagnoses; see Appendix B), and for 6 months post-vaccination for asthma and wheezing events, hospitalizations, and deaths. For rare events potentially related to wild-type influenza (see Appendix C), each vaccinee will be followed for hospitalizations and deaths until 6 months after 25,000 unique FluMist vaccinees have completed their dosing regimen (i.e., through the entire study period). For example, if the first participant is vaccinated with FluMist on 01/Oct/2007 and the 25,000th participant is vaccinated with FluMist on 31/Dec/2012, each participant will be followed for rare events potentially related to wild-type influenza from the date of that participant's first vaccination through 30/Jun/2013. MAEs of asthma in children without a prior diagnosis of asthma will also be followed through the entire study period.

Annual Revaccination

Individuals who receive two or more consecutive annual vaccinations with FluMist will be identified in the KITS database. For these individuals, rates of SAEs and other MAE endpoints will be analyzed by consecutive revaccination year (i.e., second annual revaccination, third annual revaccination) and compared to rates in first-time vaccinees during the same season.

Previous Vaccination with TIV

The safety of FluMist vaccination in children previously vaccinated with TIV will be assessed by comparing event rates among such children to rates in FluMist recipients not previously vaccinated with TIV.

6 DATA COLLECTION AND REPORTING

Computerized databases for emergency department visit, hospital admission, and outpatient clinic visit utilization at Kaiser Permanente are regularly maintained as part of routine clinical care for patients. These utilization databases are the primary resource for safety outcomes in this study.

Following each influenza season in this study, an annual interim report will be provided to the Center for Biologics Evaluation and Research by the end of September (before 01/Oct) and will include number of vaccinees, a listing of SAEs, and available event rates and risk measures. A final study report will be submitted within 1 year after complete follow-up data are available and final analyses are performed.

Deaths that occur outside the Kaiser Permanente system will be identified by review of the relevant state mortality tapes. State mortality tapes are systematically obtained by the Kaiser Permanente Vaccine Study Center and are then linked for the entire Kaiser Permanente Health Care Plan membership. Access to the mortality records will allow a comprehensive evaluation of death rates. State mortality tapes are typically available for a given calendar year 18-24 months after the end of the year. These data will be provided in a supplemental report within 6 months after the data become available.

7 HUMAN SUBJECTS

7.1 Ethics and Regulatory Considerations

The study will be conducted in accordance with the U.S. Code of Federal Regulations governing Institutional Review Boards (21 CFR 56) and Obligations of Clinical Investigators (21 CFR 312).

The protocol will be reviewed and approved by the Institutional Review Board (IRB) governing all participating centers prior to study initiation. Serious adverse events regardless of causality will be reported to the sponsor and to the IRB, and the investigator will keep the IRB informed as to the progress of the study.

To maintain confidentiality, all evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Privately identifiable information will not be released without written permission of the patient, except as necessary for monitoring by the FDA or the sponsor of the clinical trial. The principal investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996).

7.2 Institutional Review Board (IRB)

A list of IRB members should be obtained by the investigator and provided to the sponsor.

Any documents that the IRB may need to fulfill its responsibilities, such as protocol amendments or information from the sponsor will be submitted to the IRB. The IRB's written unconditional approval of the study protocol will be in the possession of the investigator and the sponsor before the study is initiated. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and the date of review.

Protocol modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted should be obtained.

The IRB must be informed by the principal investigator of revisions of documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study; new information that may affect adversely the safety of the patients or the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

7.3 Informed Consent

All participants in this study will be vaccinated in the course of obtaining routine medical care. Because this study presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research setting, obtaining

informed consent specifically for this study will not be required, in accordance with 21 CFR 56.109(c)(1).

8 STUDY COMPLETION

The study is expected to begin in the Fall of 2007 and continue until approximately 25,000 unique FluMist recipients have been vaccinated and follow-up has be completed for at least 6 months after the final dose for the final recipient has been administered.

Due to the nature of this post-marketing study, which is based on database extraction of vaccination status and medical utilization endpoints, no active termination of participants will be made. It is estimated that 2% to 5% of Kaiser Permanente members will discontinue their health plan membership annually. Therefore, some FluMist recipients may be available for only a partial assessment of post-vaccination medical utilization.

9 PUBLICATIONS

Publication by the site of any data from this study must be carried out in accordance with the clinical study agreement.

10 CHANGES IN THE PROTOCOL

The protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the FDA and IRB, and must be approved by the IRB prior to their implementation. Documentation of IRB approval must be sent to the sponsor immediately upon receipt.

Version 1.0 of the protocol (15/Jun/2007) was amended on 12/Oct/2007. Changes to the protocol are described in Appendix E and are incorporated in the body of Version 2.0 of the protocol.

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APPENDIX A Terms for Anaphylaxis

Edema of larynx

Asthma

Unspecified acute edema of lung
Acute respiratory failure
Other pulmonary insufficiency, not elsewhere classified
Acute and chronic respiratory failure

Urticaria

Syncope and collapse

Shock without mention of trauma

Shortness of breath
Tachypnea
Wheezing
Other dyspnea and respiratory abnormalities

Other anaphylactic shock not else where classified
Angioneurotic edema not elsewhere classified
Unspecified adverse effect of drug medicinal and biological substance, not elsewhere classified
Allergy, unspecified not elsewhere classified

Anaphylactic shock due to serum, not elsewhere classified
Other serum reaction, not elsewhere classified

APPENDIX B Medically Attended Events: Prespecified Grouped Diagnoses

Acute Respiratory Tract Events

Medically Attended Event	Clinic Term	Emergency Department Term	Hospital Term
Acute Respiratory Failure	Acute Respiratory Failure	Acute Respiratory Failure	Acute Respiratory Failure
ARDS	Not seen in this setting	Not seen in this setting	ARDS
Asthma/RAD	Asthma/RAD	Asthma/RAD	Asthma/RAD
Bronchitis	Bronchitis	Bronchitis	Acute laryngitis
			Acute tracheitis
			Acute laryngotracheitis
Cough	Cough	Cough	Cough
Croup	Croup	Croup	Croup
Epiglottitis	Epiglottitis	Epiglottitis	Epiglottitis
Influenza	Influenza	Influenza	Influenza with other respiratory manifestations
Influenza; Pneumonia	Influenza; Pneumonia	Influenza; Pneumonia	Influenza with Pneumonia
Mastoiditis	Mastoiditis	Mastoiditis	Mastoiditis
Otitis Media	Otitis Media	Otitis Media	Otitis Media
Pharyngitis	Pharyngitis	Pharyngitis	Pharyngitis
Pneumonia	Pneumonia	Pneumonia	Viral pneumonia
			Pneumococcal pneumonia
			Pneumonia
Sinusitis	Sinusitis	Sinusitis	Sinusitis
Tonsillitis	Tonsillitis	Tonsillitis	Tonsillitis
URI	URI	URI	URI
Wheezing/SOB	Wheezing/SOB	Wheezing/SOB	Pulmonary congestion and hypostasis
			Shortness of breath
			Tachypnea
			Wheezing

Acute Gastrointestinal Tract Events

Medically Attended Event	Clinic Term	Emergency Department Term	Hospital Term
Abdominal Pain	Abdominal Pain	Abdominal Pain	Abdominal Pain
			Paralytic ileus
			Peritonitis
Acute Gastroenteritis	Acute Gastroenteritis	Acute Gastroenteritis	Acute gastritis
			Acute Gastroenteritis
			Persistent vomiting
Appendicitis	Appendicitis	Appendicitis	Appendicitis
Intestinal Obstruction	Intestinal Obstruction	Intestinal Obstruction	Intestinal Obstruction
Intussusception	Intussusception	Intussusception	Intussusception
Irritable Bowel Syndrome	Irritable Bowel Syndrome	Irritable Bowel Syndrome	Irritable Bowel Syndrome
Mesenteric Adenitis	Mesenteric Adenitis	Mesenteric Adenitis	Mesenteric Adenitis
Nausea and vomiting	Nausea and vomiting	Nausea and vomiting	Nausea and vomiting
Pancreatitis	Pancreatitis	Pancreatitis	Pancreatitis
Perforation of Intestine	Perforation of Intestine	Perforation of Intestine	Perforation of Intestine
Small Bowel Obstruction	Small Bowel Obstruction	Small Bowel Obstruction	Small Bowel Obstruction
Ulceration of Intestine	Ulceration of Intestine	Ulceration of Intestine	Ulceration of Intestine
Volvulus	Volvulus	Volvulus	Volvulus

APPENDIX C Medically Attended Events: Rare Events Potentially Related to Wild-type Influenza Infection

Medically Attended Event	Clinic Term	Emergency Department Term	Hospital Term
Encephalitis/ encephalopathy	Encephalitis/ encephalopathy	Encephalitis/ encephalopathy	Encephalitis/ encephalopathy
Guillain-Barre syndrome	Guillain-Barre syndrome	Guillain-Barre syndrome	Guillain-Barre syndrome
Meningitis	Meningitis	Meningitis	Meningitis
	Viral Meningitis	Viral Meningitis	Viral Meningitis
Myocarditis	Myocarditis	Myocarditis	Myocarditis
Other paralytic syndromes	Not Seen in this Setting	Not Seen in this Setting	Other paralytic syndromes
Pericarditis	Pericarditis	Pericarditis	Pericarditis
Polymyositis	Polymyositis	Polymyositis	Polymyositis
Reye Syndrome	Reye Syndrome	Reye Syndrome	Reye Syndrome

APPENDIX D Immunosuppressive Conditions in Children

Chronic renal insufficiency

Collagen vascular diseases

Hematologic malignancies
Solid organ malignancies

Radiotherapy
Chemotherapy

Human immunodeficiency virus (HIV) disease

Hypogammaglobulinemia, unspecified
- Agammaglobulinemia, unspecified

Selective IgA immunodeficiency
Selective IgM immunodeficiency
Other selective immunoglobulin deficiencies
- Selective deficiency of IgG

Congenital hypogammaglobulinemia
- Agammaglobulinemia
- Bruton's type
- X-linked

Immunodeficiency with increased IgM
- Immunodeficiency with hyper-IgM
- Autosomal recessive
- X-linked

Common variable immunodeficiency
- Dysgammaglobulinemia (acquired)(congenital)(primary)
- Hypogammaglobulinemia
- Acquired primary
- Congenital non-sex-linked
- Sporadic

Other immunodeficiency
- Transient hypogammaglobulinemia of infancy

Immunodeficiency with predominant T-cell defect, unspecified

DiGeorge's syndrome
- Pharyngeal pouch syndrome
- Thymic hypoplasia

Wiskott-Aldrich syndrome

Nezelof's syndrome
- Cellular immunodeficiency with abnormal immunoglobulin deficiency

Combined immunity deficiency
- Agammaglobulinemia
- Autosomal recessive
- Swiss-type
- X-linked recessive
- Severe combined immunodeficiency (SCID)
- Thymic alymphoplasia
- Aplasia or dysplasia with immunodeficiency

Unspecified immunity deficiency
Autoimmune disease, not elsewhere classified
- Autoimmune disease NOS

Other specified disorders involved in the immune system
- Single complement (C1-C9) deficiency or dysfunction

Unspecified disorder of immune mechanism

Functional disorders of polymorphonuclear neutrophils
- Chronic (childhood) granulomatous disease
- Congenital dysphagocytosis
- Job's syndrome
- Lipochrome histiocytosis (familial)
- Progressive septic granulomatosis

Organ or tissue replaced by transplant
- Kidney
- Heart
- Heart valve
- Skin
- Bone
- Cornea
- Lung
- Liver
- Bone marrow
- Peripheral stem cells
- Pancreas
- Intestines

APPENDIX E Changes to the Protocol

Version 2.0, 12/Oct/2007

All text revisions resulting from this amendment are incorporated in the body of the protocol in Version 2.0. Major changes to the protocol are described below.

1. Throughout the protocol: Reference to MedImmune Vaccines, Inc., and MedImmune, Inc., was changed to "MedImmune" to more accurately reflect the sponsor's designation.
2. Study Abstract: The abstract was revised to be consistent with the text of the protocol as described below.
3. Section 1.2 (Description of FluMist): US FDA approval for use of FluMist in children 24-59 months of age in September 2007 was added.
4. Section 2.1 (Objectives), Section 3.1.1 (FluMist Recipients), and Section 5.4 (Endpoints): Objective #4 and the accompanying footnote were deleted, along with the endpoint of "effectiveness of the Risk Minimization Action Plan." All reference to substudies of MI-MA162 (evaluation of data for FluMist recipients who are less than 24 months of age, who are 24-59 months of age with a probably history of asthma/RAD/recurrent wheezing, or 24-59 months of age with immunosuppression) were deleted per re-negotiated post marketing commitments with US FDA. These objectives will be met by a separate study not associated with MI-MA162.
5. Section 3.3.1 (Vaccine Supplies and Accountability): This section was revised to state that FluMist will be commercially obtained by Kaiser Permanente.

Version 3.0, 04Jun2008

All text revisions resulting from this amendment are incorporated in the body of the protocol in Version 3.0. Major changes to the protocol are described below.

1. Section 5.1 (General Considerations): The statement "safety comparisons will also be performed using the Cox proportional hazards model implementing the counting–process style of input (Andersen and Gill 1982)" has been changed to "safety comparisons will also be performed using the Cox proportional hazards model implementing the counting–process style of input (Andersen and Gill 1982) or a similar method".