

Delivery Science and Applied Research: Project Proposal Outline

A. Project Description:

Project Title: (similar to manuscript title)	Association Between Spinal Injection of Corticosteroids and Risk for Influenza	
Specialty/Subspecialty:	Physical Medicine / Pain Management	
Principal TPMG investigator:	Joshua Rittenberg	
Your Medical Center:	Oakland	Date: 12/18/2020
Specialty Chair of Chiefs:	Joshua Rittenberg / Darshan Patel	Approving AED: Smita Rouillard and Sameer Awsare

***For each question, provide 2-4 sentences *(approximate box size). An example is provided for level of detail.**

1. What is the challenge you are addressing? Include how common the problem is and its impact.

Injected corticosteroids are commonly used in treatment for many acute and chronic pain conditions. We estimate that over 50,000 epidural corticosteroid injections are administered per year to KP NCAL patients. The question is whether administration of corticosteroids via epidural / intraspinal routes increases the risk for influenza. Many of our spine patients are elderly or have co-morbidities that may place them at increased risk. We currently do not know if receiving a corticosteroid injection places these patients at higher risk for influenza and severe illness compared with a similar population not receiving corticosteroid injections. Addressing the question about effect of injected corticosteroids would be an important one in determining risk versus benefit when these procedures are being considered for this population. There is currently no published literature that addresses this question.

2. What is the existing evidence for solving this problem (trials or observational studies)? Include if current evidence is sufficient to inform implementation or if new knowledge/investigation is needed and, if so, what knowledge.

Several studies describe a reduction in immune response following intraarticular corticosteroid administration. Our co-investigators from Mayo - Sytsma and Greenlund, published a large retrospective study (n>15,000 pts) in 2018 demonstrating that the risk for influenza is increased in patients receiving an intraarticular (non-spinal) corticosteroid injection just before or during flu season, even in vaccinated patients. They are currently analyzing data to address this same question in patients receiving spinal injections. In addition to the prior published study, they have a pending publication that includes potential confounders and co-morbidities that will need to be accounted for in our study. The KP study would provide a broader and more diverse population and would significantly increase the number of procedures and patients included in this overall analysis. There are no published studies describing the effect of spinal corticosteroids on influenza risk.

3. What specific clinical actions/changes are anticipated from addressing the challenge? Include any technology, nursing, or tracking needed, and all specialties impacted. If new knowledge is needed, are existing KP data sufficient or are new data required (and, if so, what)?

By addressing this question, physicians will be better able to assess risk vs benefit in recommending or providing spinal corticosteroid injections to their patients who may be considered at risk for influenza. We hope to develop a risk assessment tool that could help clinicians in decision making prior to spinal injection procedures. Specialties that will be impacted include the many specialties that provide or refer for epidural or other spinal corticosteroid injections: primary care, physical medicine and rehabilitation, pain management, anesthesiology, orthopedics, sports medicine, rheumatology, and radiology.

It is likely that we will be able to find this data within KPHC with adequate analytical support. Our challenge in obtaining this data will be in determining which patients received corticosteroid injections and dosing of corticosteroid injections. Much of this data may be contained within progress or procedure notes, and it is likely that CPT coding for office-based procedures may be inconsistent. It will also be challenging to identify patients with influenza and patients who received a vaccine during the period to be studied.

4. If the challenge is addressed, has commitment for the actions been obtained by relevant regional clinical leaders?

This area has been identified as a clinically important area by the Chiefs of Physical Medicine and Rehabilitation and by the Chiefs of Pain Management.

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B. Research Team Members:

Main Study Team:

	Name
Principal Research Scientist:	Julie Schmittiel
Primary data analyst:	Brandon Horton
Others (name and role):	Mamie Air (co-investigator, PM&R Chief SRF)

Key Stakeholders:

	Name
Other relevant AED:	Smita Rouillard / Sameer Awsare
Other relevant specialty Chair of Chiefs:	Joshua Rittenberg / Darshan Patel
Other key stakeholders and titles:	

C. Methods/ Analytic Plan

General Study Type:

- Cross-sectional (associations at one point in time) Case-control (comparing disease vs. non-diseased)
 Cohort (comparing risks of outcome over time) Clinical trial including cross-over

Population of interest for study (incorporate inclusion and exclusion criteria):	Adults, age 18 and older who have membership during any of the windows of September – April from 2009-2019 (encompassing 10 flu seasons and allowing for a 30-day injection look-back window prior to the start of each season). Please note we will not include 2019-2020 due to the many confounding effects of COVID-19 and shelter-in-place rules. Stratified by influenza vaccination status (vaccinated vs. unvaccinated)
Intervention/exposure data elements and any measurements (survey, chart review, etc.):	Received a spinal corticosteroid injection during the observation windows
Comparison population:	Patients in KPNC who did not receive a spinal injection during the influenza season of the year of interest
Outcomes of interest:	Incidence of influenza in patients receiving spinal corticosteroids vs. control group <ul style="list-style-type: none"> - Call center data (URI/flu symptoms) - Outpatient management (mild, not requiring ED or hospitalization) <ul style="list-style-type: none"> o Telephone or online management o Rx for Tamiflu o Lab result positive for influenza o Symptoms (fever, body aches, sore throat, cough) - Visit to Emergency Department for flu or flu like illness - Hospitalized for flu or flu like illness

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Data collection approach/data elements (list existing and new data elements, surveys and chart reviews needed)

Data will be derived from existing KPNC research databases (Clarity, VDW, registries, etc.). No primary data collection will be needed. Chart review will be done on an as-needed basis for quality assurance of data extraction.

Key data elements include:

- Identification of patients in KPNC who received a spinal injection as defined by procedure codes in Appendix A
- Filtered operative/procedural reports for mention of corticosteroids to exclude patients not receiving corticosteroids
- Influenza vaccination status during year of inclusion based on procedure codes in Appendix A
- Influenza diagnosis during year of inclusion using ICD codes in Appendix B

Statistical analysis strategy; include potential confounders, effect modifiers, sample size and power calculations

Primary Analysis: Incidence of influenza in patients who received corticosteroids compared to general population

Stratified Analyses: Incidence of influenza in patients who received corticosteroids, stratified by influenza vaccination in the year of observation

Multiple logistic regression will be utilized to assess the association between known risk factors and influenza infection.

Confounding variables: Age, sex, race, BMI, corticosteroid dosage, number of injections, census/socioeconomic status, service area, history of influenza vaccination in prior years, ICD-coded comorbidities including diabetes, renal disease, COPD, IBD, HIV, Heart Failure, CLL, Myeloma, Rheumatoid Arthritis, Other Autoimmune, Cirrhosis, and Transplant (Appendix B), flu season year

Power calculation: If the incidence of influenza in our population is roughly 5%, then we would need around 4000 cases(corticosteroids+influenza dx) to see a 1% increase in incidence in the study group compared to the general population (assuming an alpha of 0.05 and 80% power). We expect to have more than sufficient power to address the study question

- Potential limitation is comparison patients receiving non-spinal injection or systemic corticosteroids

Report presentation plans (data elements, figures; attach table shells including consort-type diagram for population):

Table 1: Demographic and Clinical characteristics, overall and by year

Figure 1: Patients receiving spinal injections and incidence of influenza by year

Table 3: Logistic regression results overall and stratified by influenza vaccination status in year of measurement

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Deliverables (include clinical actions described in Section A, manuscript title(s), reports, presentations, IT products, and other expected products. Include any innovations, and if results might be generalizable to other situations:

Manuscript
 Presentation at national conference
 Influenza risk among spinal injection patients risk assessment tool and messages to assist in clinical decision making, based on findings

Internal/Regional Dissemination Plan (include role of clinical or regional champions, others):

Material will be shared with all stakeholders, including PM&R, Pain Management, Spine Surgery, Physical Therapy, and Adult and Family Medicine.
 This will occur via powerpoint presentation and other written summary material
 Dissemination will be facilitated by the Chiefs of PM&R and Pain Management.

Regional Implementation Evaluation Plan. (include metrics for evaluating success of implementation):

Future evaluations can focus on measuring the % of clinicians and facilities that adopt guidelines based on results (e.g. % of patients receiving spinal injections who receive an influenza vaccine)

Manuscript Writing Group (also to include analysis team as co-authors):

	Name	Affiliation	E-mail Address
Lead author:	Mamie Air	San Rafael Medical Center	Mamie.Air@kp.org
Senior author:	Joshua Rittenberg	Oakland Medical Center	Joshua.D.Rittenberg@kp.org
Coauthor:	Julie Schmittdiel	Division of Research	Julie.A.Schmittdiel@kp.org
Coauthor:	Brandon Horton	Division of Research	Brandon.H.Horton@kp.org
Coauthor:			

D. Proposed Timeline, Milestones and Effort:

Project start date	January 4 th 2021
Finalize variable definitions	March 1 st 2021
Complete data acquisition	April 1 st 2021
Other tasks (e.g. record review)	
Complete analysis	July 2021
Complete manuscript/report	August 2021
Expected RAU scientist hours	10% FTE
Expected analyst hours	25% FTE

Key References (can continue on separate page):



SystemaCorticosteroi
dsInfluenza.pdf

- Sytsma T, Greenlund LK, Greenlund LS. Joint corticosteroid injection associated with increased influenza risk. *Mayo Clin Proc Inn Qual Out.* June 2018;2(2):194-198
- Habib G, Jabbour A, Artul S, Hakim G. Intra-articular methylprednisolone acetate injection at the knee joint and the hypothalamic-pituitary-adrenal axis: a randomized controlled study. *Clin Rheumatol.* 2014;33(1):99-103.
- Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. *Nat Rev Immunol.* 2017;17(4):233-247.
- Hollander JL, Brown EM Jr, Jessar RA, Brown CY. Hydrocortisone and cortisone injected into arthritic joints: comparative effects of and use of hydrocortisone as a local antiarthritic agent. *J Am Med Assoc.* 1951;147(17):1629-1635.

Date of Review: _____

Action:

- Approved AED and committee Not Approved
- Conditionally Approved, reason: _____