Biostatistics Scope of Work Agreement

General Information

Investigator	Kristen Demourelle Kristen.demourelle@ucdenver.edu	**Date**	August 9, 2018
Project Number	P1363Demourelle		
Project Title	Mediation analysis of anti-CCP data in RA studies		

Understanding of Project

Project Description

Overview: Anti-cyclic citrullinated peptide (anti-CCP) antibodies are prevalent in individuals with rheumatoid arthritis (RA), and are often present early in the disease process. These antibodies target the citrullinated protein, which are found in people's joints, however, little is known about the biologic pathways influencing anti-CCP production. One hypothesis is that citrullinated proteins expressed on neutrophil extracellular traps (NETs) in the lung will trigger the production of anti-CCP. When a neutrophil net's, it releases various components such as MPO, Histones, and Elastase. NETs are thought to be triggered by cytokines/chemokines (e.g. IL-6, TNFa, etc) and antibodies (RF-IgA, CCP). To better understand the relationships between simulants of NET activity, NET activity itself, and anti-CCP, the investigators propose to conduct a mediation analysis to evaluate the direct and indirect effects of various NET stimulants on anti-CCP production, through NET activity. CIDA will conduct mediation analyses and provide a written report of findings, participate in the preparation of the manuscript.

Description of the Data and Variables: The investigators have obtained cross-sectional data for potential exposure, mediator, and outcome information on approximately 35 individuals.

Variables of interest for this analysis have been categorized using an

X -> M -> Y

notation, where X are potential exposures, M are potential mediators, and Y is the outcome of interest.

Potential Exposures (X): A panel of 9 cytokines/chemokines were measured on all subjects. A few are associated with CCP (IL6, IL8 and IL10), and a few are associated with measurements of NETosis, and many of individual measurements will be highly correlated. It is common in RA studies to evaluate a panel of cytokines using a summary measure (e.g. weight or score the cytokines), as there can be different cytokines in different people which result in the same biologic function. In addition to cytokines, RF-IgA is a known trigger for NET activity, and will be evaluated as a potential exposure. In total, we propose to evaluate:

- 1-2 individual cytokines of interest
- One form of an overall group measure of the cytokines (e.g. first principal component, or some other weighted average)
- RF-IgA

Measurement of NET activity (M's): Net activity in vivo may be measured by ELISA, which assess the NET remnant levels by DNA-protein complexes (DNA-MPO, DNA-NE, and DNA-cit-histone H3). The potential to NET can be measured ex vivo by harvesting cells and calculating the % of cells which NET after stimulant. The investigators have evaluated univariate associations between various factors and the potential to NET but will not evaluate these in the mediation models. In total, we propose to evaluate 3 potential mediators:

- DNA-cit-histone H3 (primary mediator of interest)
- DNA-MPO (secondary mediator)
- DNA-NE (secondary mediator)

Outcome (Y): anti-CCP levels will be evaluated as the only outcome of interest.

Potential Confounder: Smoking is known to affect chemokine/cytokine levels as well as have many other negative impacts on physiological functioning. There are only a few current smokers, but approximately 30% are former smokers. A dichotomized current/former smoking variable should be explored as a potential confounder to these models.

Deliverables: Under this contract, CIDA will conduct mediation analyses for the variables outlined above and provide the following:

- Exploratory Report: this report will provide some initial descriptive statistics and relationships, and specifically explore the relationships among cytokines in order to guide a choice for the overall summary measure for the panel.
- Comprehensive Report: this report will contain a near-publication-ready statistical methods section and results section for the mediation analyses.
- Manuscript Preparation: the CIDA biostatistical team will assist in writing the methods and results sections pertaining to the mediation analyses, as well as review and provide feedback on other sections as appropriate.

Additional Notes for the Biostatistical Team:

- We are proposing to test up to 4 potential predictors and 3 mediators, resulting in a total of 12 mediation models. Multiple comparisons is an issue that should be considered and accounted for. One option is to propose a single primary hypothesis (e.g. association between overall group measure of cytokines and anti-CCP is mediated through DNA-cit-histone H3), and then correct on all secondary / exploratory hypotheses. Alternatively, if all hypotheses are deserving of equal weight an interest, then a correction on all should be conducted.
- The investigators have conducted many analyses (e.g. univariate and correlation testing) and will include those in the manuscript. CIDA will not duplicate those analyses, but should review them; if the investigator needs additional analyses or evaluations, the CIDA administrative team should be notified as an addendum to the SOW may be necessary.
- The investigators have asked about presenting the individual relationships between all cytokines and anti-CCP, and cytokines and NET values – there are a lot of comparisons and they want to consider both getting new information out, without overwhelming the manuscript. One suggestion is to present correlations without p-values, while another is to present with FDR adjusted p-values but downplay any statistical inference and just put focus on the observed data.

Timelines/Deadlines

The investigators are currently working on a paper and would like to submit as quickly as possible. Assuming there are no unforeseen issues with the data and that communications between the investigator and biostatistical team are timeline (email responses within 1 business day), these analyses are anticipated to take approximately 4 working weeks and no more than 6. Upon approval of the scope of work, a biostatistical team will be assigned and a kickoff meeting will be scheduled; the target is to schedule the kickoff meeting within one week of team assignment. During the kickoff meeting, a meeting date for review of the exploratory data analysis will be established. Similarly, during the exploratory review meeting, a meeting date for the review of the comprehensive analysis will be established.

Project Cost and Milestones

Project Type: Average Data Analysis/Publication

Billing Phase and Milestone	Cost
Phase 1: Project Start Up Discuss and review project materials, establish timelines, deliverables, and data structures with biostatistician.	$ 450
Phase 2: Exploratory Analysis Establish preliminary analysis dataset, run descriptive statistics and graphics, and create a report.	$ 3525
Phase 3: Comprehensive Analysis Complete comprehensive analysis and present a report. Additional changes to analysis are anticipated and part of the Project Complete phase.	$ 3525
Phase 4: Project Complete Complete final analysis and publication quality figures.	$ 450
Customization:	0
Total Due	**$ 7950**

Approval of Agreement

By approving this Scope of Work Agreement, you are acknowledging that you have read and agree to the project costs and milestones, timelines, project details, and terms and conditions outlined in this document.

To approve this Scope of Work Agreement click the button below.

Approve Scope of Work Agreement

(If you don't agree with this Scope of Work Agreement or would like to withdraw your request for CIDA services, please send us an email to cida@ucdenver.edu with a brief explanation.)

Terms and Conditions

Clean data requirements - ready for analysis

The data are assumed to be cleaned and ready for analyses unless otherwise agreed upon, and a data dictionary should be provided to the analyst. We strongly encourage the use of REDCap as a data collection and management tool.

Report writing, abstract and manuscript preparation and revision

A final report will be created with an introduction, statistical methods, and results section. These sections will be close to publication ready. The CIDA biostatistician will edit the methods and results section for publication and read the final version of the manuscript prior to submission. Assuming the biostatistician has provided significant contribution to the manuscript in terms of performing analyses and contributing to the results and methods sections, the biostatistician shall be a co-author on the publication, acknowledging the intellectual contribution of the work.

Assuming no substantial new analysis is needed, the CIDA biostatistician will assist with writing a response to reviewer's statistical questions, make revisions to the paper and review the final version of any revised manuscript. If substantial new analysis is required, a new scope of work will be created and with costs agreed upon by both parties.

CIDA Authorship Guidelines

The CIDA abides by the International Committee of Medical Journal Editors (ICMJE) guidelines concerning authorship. Visit our CIDA website to learn more about CIDA's authorship policies.

Specific CIDA guidelines include:

- The biostatistician performing the analysis will be a co-author on the publication to acknowledge the intellectual contribution to the work. Statistician co-authors will use their primary appointment affiliation on manuscripts and abstracts.
- To maintain study and statistical integrity, data collected for publication and abstracts will only be analyzed after study completion.
- The CIDA biostatistician performs the analysis, collaborates in the structuring of the presentation of the results, and writes the "statistical methods" section of the paper.
- The biostatistician reviews the publication and any revisions prior to submission.
- The biostatistician will assist with revisions, keeping in mind your revision deadlines.

CIDA's right to cancel or close out a project

Please approve the Scope of Work (SOW) within 15 days (or prior to anticipated start of work, if less). SOWs not approved within 30 days will be closed. Projects which remain inactive for over 60 days will be closed unless prior arrangements have been made, and a final bill will be sent for work completed.

CCTSI subsidized projects

If the project cost is subsidized by the Colorado Clinical and Translational Sciences Institute (CCTSI), you are required to cite the CCTSI grant in posters and publications. Please review the CCTSI's Citation and CTSA grant language.