**Principal Investigator**

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**General Information**

Key Personnel (other than PI):

<table>
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<tr>
<th>First Name</th>
<th>Last Name</th>
<th>Degree</th>
<th>Primary Affiliation</th>
<th>SCOPUS ID</th>
<th>Requires Data Access?</th>
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<tr>
<td>Nermin</td>
<td>Diab</td>
<td>MD, MPH</td>
<td>McMaster University</td>
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<tr>
<td>Alejandro</td>
<td>Chu</td>
<td>Medical Student</td>
<td>McMaster University</td>
<td></td>
<td>Yes</td>
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<tr>
<td>Lehana</td>
<td>Thabane</td>
<td>BSc, MSc, PhD</td>
<td>McMaster University</td>
<td></td>
<td>Yes</td>
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**Are external grants or funds being used to support this research?:** No external grants or funds are being used to support this research.  
**How did you learn about the YODA Project?:** Colleague

**Conflict of Interest**


**Certification**

**Certification:** All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.  
**Data Use Agreement Training:** As the Principal Investigator of this study, I certify that I have
completed the YODA Project Data Use Agreement Training

1. NCT00207740 - A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging Study Evaluating the Efficacy and Safety of CNTO 148 Administered Subcutaneously in Symptomatic Subjects With Severe Persistent Asthma

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Efficacy and safety of monoclonal antibodies in patients with uncontrolled asthma: a systematic review and network meta-analysis.

Narrative Summary:

Asthma is a lung disorder that affects millions of individuals across the world. It is characterized by symptoms of reversible shortness of breath and wheezing. While most asthma is treated with inhaled medications (medicines that you breathe in), mainly inhaled steroids, some asthmatics have severe symptoms that are not relieved with conventional therapy and require certain injected molecules (substances introduced into the body by injection) for the treatment of their severe asthma. These injectable molecules are called "biologics", which are drugs that are derived from living organisms or "monoclonal antibodies", which are molecules designed to mimic the immune system's ability to fight off harmful pathogens. There are currently multiple biologics approved for the treatment of asthma. However, data on their safety and efficacy when compared to each other is lacking. This study aims to compare the safety and efficacy of biologics used to treat severe asthma through a research methodology called network meta-analysis (NMA). This methodology of research will allow the comparison of various biologics to each other, even if they have not been studied directly against each other in real life.

Scientific Abstract:

Background: There are currently no trials directly comparing biological therapies in asthma. The choice of a biologic is typically made based on patients’ asthma phenotype.

Objective: We aim to collect the data on biologics from already published randomized control trials in order to analyse the data in a way that would allow us to make direct comparisons of the safety and efficacy of biologics.

Methods: We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), US Food and Drug Administration (FDA), and European Medicines Agency (EMA) databases from inception to March 2024 for randomised control trials comparing biological therapies to placebo, standard of care or other biological therapies. We screened studies, extracted data, and assessed risk of bias in duplicate.

Primary Outcomes analysed will include asthma exacerbations, serious adverse events, adverse events leading to drug discontinuation, mortality, asthma control and asthma related quality of life. Statistical analysis: We will perform a frequentist network meta-analysis and use the GRADE approach to assess the quality of evidence. This study is registered with PROSPERO number CRD42023330894.

Brief Project Background and Statement of Project Significance:
We aim to collect the data on biologics from already published randomized control trials and compile the data for each biologic. The network meta-analysis is a technique that will allow comparing three or more interventions simultaneously in a single analysis by combining the evidence and data collected across studies. The data requested to be collected will allow us to gather more evidence for each biologic molecule and will ultimately help us accumulate the data to answer our question. We plan to combine summary level results for each biologic molecule. Given that in real life it is impossible to run head to head trials of all biologics, a network meta-analysis will allow us to make this comparison with compiled data per biologic (i.e. we will compile data per biological molecule and regard it as a single intervention when comparing it to another biologic molecule). However, each study in which data has been requested will be used separately when we perform a systematic review, as well as when we are assessing the risk of bias of that specific study.

**Specific Aims of the Project:**

The main question of this proposed research is: In patients with uncontrolled asthma, what is the efficacy and safety of monoclonal antibodies compared to one another when added to standard of care, and when compared to standard of care alone?

The specific aim of this research is to compare and evaluate the safety and efficacy of all biologics used in asthma. We will be performing a systematic review and network meta-analysis with patient level data to evaluate the outcomes described below as well as the subgroup analysis. For the subgroup analysis, our hypothesis is the following:
1. We hypothesize that the relative effect of biologics will be greater in older patients compared to younger patients.
2. We hypothesize that the relative effect of biologics is greater in patients with higher blood eosinophil counts compared to patients with lower blood sputum eosinophil counts.
3. We hypothesize that the relative effect of biologics is similar irrespective of whether a trial was a cross over or a parallel group design but that the cross over studies may lead to counterintuitively narrow CIs.
4. We hypothesize that the relative effect of biologics may be greater in withdrawal vs. add on therapy studies.
5. We hypothesize that the relative effect of biologics is greater with higher doses compared to lower doses.
6. We hypothesize that the relative effect of biologics is greater with intravenous versus subcutaneous formulation.

**Study Design:**

Meta-analysis (analysis of multiple trials together)

**What is the purpose of the analysis being proposed? Please select all that apply.**

- Participant-level data meta-analysis
- Meta-analysis using data from the YODA Project and other data sources

**Research Methods**

*Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:*

Published or unpublished randomized controlled trials of any size and in any language that compare monoclonal antibodies against placebo, standard of care, or another monoclonal antibody for treatment of asthma.
We will exclude review articles, commentaries, pharmacokinetic, pharmacodynamic and mechanistic studies, methodological articles; cross-sectional studies; cohort studies; reports only presented as conference abstracts unless they are conference abstracts from 2021 or 2022 of RCTs anticipated to be published in full publication form within the subsequent 12 months; studies exclusively evaluating pediatric patients less than 6 years old, pregnant patients; and studies with no comparison group.

We will include patients with moderate to severe asthma who have been studied in these trials of ages 6 years and older, both male or female, who have received either the active treatment or placebo.

**Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:**

**Main outcome(s)**

1. Moderate/severe asthma exacerbations, defined by any of the criteria below: (one or more exacerbation, and number of events (annualized exacerbation rates).
   - Systemic corticosteroid use for asthma exacerbation
   - Emergency department visit for asthma exacerbation
   - Hospitalization for asthma exacerbation
   - Intensive care visit or intubation for asthma exacerbation
   - If reported only as a composite outcome, then this will also be accepted. We will attempt to obtain all individual components from study authors.

2. Asthma control eg. Asthma control questionnaire, with preference from highest to lowest being Asthma Quality of Life Questionnaire 5 (ACQ5), Asthma Quality of Life Questionnaire 6 (AC6), then tools such as Asthma Control Test (ACT) or Asthma Quality of Life Questionnaire 7 (AC7).

3. Any asthma health-related quality of life measure, eg. Asthma Quality of Life Questionnaire (AQLQ)

4. Adverse outcomes (each will be analyzed separately.):
   - Serious adverse events (includes mortality).
   - Discontinuation due to adverse event.

**Main Predictor/Independent Variable and how it will be categorized/defined for your study:**

We will include studies including patients 6 years of age or older, with confirmed diagnosis of asthma (mild, moderate and severe). Intervention will include any monoclonal antibodies used for treatment of asthma. Comparator will include placebo, standard of care, or another monoclonal antibody.

**Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:**

We are also requesting IPD (individual patient level data) to perform subgroup analysis of these outcomes including baseline:

1. Age (eg. < 18 vs 18+)
2. Baseline eosinophil level
3. Body Mass Index (BMI)
4. Number of previous asthma exacerbations
5. Presence of absence of nasal polyps
6. Allergic vs. non allergic asthma
7. FeNO levels (fractional exhaled nitric oxide)
8. Race
9. Baseline asthma control questionnaire scores (ACQ)
10. Baseline Asthma quality of life data (AQLQ)

**Statistical Analysis Plan:**

Measures of effect
Absolute and relative risks with 95% confidence intervals will be used for the outcomes outlined above, displayed using forest plots and calculated using random effects models. Continuous outcomes will be summarized as between group mean differences.

We will summarize dichotomous outcomes as relative risks, and continuous outcomes using mean differences. The preferred value to pool for continuous outcomes will be changes from baseline, with those estimated using analysis of covariance (ANCOVA) adjusting for at least baseline values preferred over unadjusted estimates.

We will perform conventional meta-analysis using random-effects models in Review Manager (v5.4) and statistics and data (STATA) (version 14 or above). In the case when random effects models lead to counterintuitive results, we will switch to a fixed effects model.

We will perform a frequentist random-effects network meta-analysis to assess the relative effect of all interventions simultaneously. We will use the netmeta package of R version 3.4.3 (R Core Team, Vienna, Austria) to perform the network meta-analysis.

We will address publication bias using a comprehensive search, relationship of funding to study findings, and examining for strong evidence of small-study effects in comparison-adjusted funnel plot of treatment estimates.

Analysis of subgroups or subsets
We will explore prespecified hypotheses to examine heterogeneity using subgroup or (network) meta-regression analyses in a random-effects mode with preference, where applicable, for participant-level subgroup data over trial-level comparisons (ie. within rather between trial analyses). Hence, we are requesting patient level data.

Each study in which data has been requested will be used separately when we perform a systematic review, as well as when we are assessing the risk of bias of that specific study.

Software Used:

R

Project Timeline:

We anticipate obtaining the data in May 2024 and completing analysis by June/July 2024

Dissemination Plan:

The manuscripts resulting from this project will be submitted to journals such as BMJ, Lancet and AJRCCM. Data will also be used to inform producing guidelines.