Protocol for Systematic Review and Meta-Analysis on the Efficacy and Safety of Tocilizumab


1Program of Clinical Pharmacy, College of Pharmacy, Al Ain University, Al Ain-UAE.Email:assahura2021@gmail.com; ORCID https://orcid.org/0000-0003-4143-7810.
2Program of Clinical Pharmacy, College of Pharmacy, Al Ain University, Al Ain-UAE. Email: adel.sadeq@aau.ac.ac; ORCID https://orcid.org/0000-0001-9529-8898.
3Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, Center of Medical and Bio-allied Health Sciences Research, Ajman University, Ajman-UAE. Email: f.hamad@ajman.ac.ae; ORCID https://orcid.org/0000-0003-3339-9743.
4Clinical Pharmacist, Omdurman Islamic University, Omdurman-Sudan. Email: israamak81@gmail.com; ORCID https://orcid.org/0000-0001-8674-3603.
5Pharmacist; Abu Dhabi Health Services, Abu Dhabi-UAE Email: doaa.nassar000@gmail.com ORCID: https://orcid.org/0000-0003-0833-1341.
6Teaching Assistant, Faculty of pharmacy, Managel University for Science and Technology, Managel, Sudan.Email:isamsangac@gmail.com; ORCID: https://orcid.org/0000000345132333.
7Pharmacist, Abu Dhabi Health Services, Abu Dhabi-UAE. Email: jalaryani1828@yahoo.com; ORCID https://orcid.org/0000-0002-3806-8583.
8College of Pharmacy, Gulf Medical University, Ajman-UAE. Email: juditied28@gmail.com; ORCID https://orcid.org/0000-0003-3066-5962.
9Clinical Pharmacist, Sheikh Shakhbout Medical City, Abu Dhabi-UAE. Email: MohamEelahmin5005@gmail.com; ORCID: https://orcid.org/0000-0002-7118-827X.
10Nadeen Ali, Clinical Pharmacy Lecturer, Department of Pharmacology, College of Pharmacy, University of Khartoum, Khartoum, Sudan. Email: nadeentaajalisi@gmail.com; ORCID: 0000-0002-5105-5891.
11Pharmacist, Al Murabaat Pharmacy, Khartoum, Sudan; Email: salma.magboul2015@gmail.com; ORCID https://orcid.org/0000-0003-1699-2123.
12Pharmacist; Abu Dhabi Health Services, Abu Dhabi-UAE Email: nkassem72@gmail.com; ORCID https://orcid.org/0000-0002-4225-7870.
13Pharmacist; Abu Dhabi Health Services, Abu Dhabi-UAE Email:haia_abdulsamad@hotmail.com ; ORCID: https://orcid.org/0000-0001-9395-3254.
14Clinical pharmacist. University of Khartoum-Sudan. Email: salahwar83@gmail.com; ORCID https://orcid.org/0000-0003-1423-3174.
15Clinical Preceptor, Ibn Sina University, Khartoum-Sudan. Email: ekrimasadan@gmail.com; ORCID: https://orcid.org/0000-0001-5230-0476.
16Clinical Pharmacist, Ministry of Health, Aldamer Teaching Hospital. Aldamer-Sudan. Email: hanan4u2@yahoo.com; ORCID: http://orcid.org/0000-0002-6516-4685.
17Clinical Pharmacist Independent Researcher. Email: hagaramaw1213@gmail.com; ORCID: https://orcid.org/0000-0002-3395-843x.
18Dentist, MySmile Dental Clinic, Dubai, UAE. Email:alsahura1995@hotmail.com. ORCID https://orcid.org/0000-0002-6052-5883.
19Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin, Republic of Ireland. Email: sadeqa@tcd.ie; ORCID: https://orcid.org/0000-0001-8540-0588.
20Department of Medical Imaging and Radiation Sciences, Monash University, Email:abubakar.abubakar@monash.edu, ORCID: https://orcid.org/0000-0002-0922-572x.
21Assistant Professor, Medical Laboratory Sciences College of Health Sciences Gulf Medical University, Ajman-UAE. Email: dr.abdel@amu.ac.ae; ORCID https://orcid.org/0000-0002-2442-2756.
22Ambulatory Healthcare Services, Academic Affairs, Abu Dhabi Health Services (SEHA), UAE. Email: aalamoodi@seha.ae; ORCID: https://orcid.org/0000-0001-5248-9598.
23Clinical Pharmacy, College of Pharmacy, Riyadh Elm University Riyadh-Saudi Arabia. Email: sashaburass@gmail.com. ORCID: https://orcid.org/0000-0002-0226-0602
24Department of Epidemiology and Population Health, Khalifa University, Abu Dhabi-UAE. Email: nalahjri007@gmail.com; ORCID: https://orcid.org/0000-0001-7205-7493

Corresponding Author: Asim Ahmed Elnour Program of Clinical Pharmacy, College of Pharmacy, Al Ain University, Al Ain-UAE. Email:assahura2021@gmail.com
Impact of findings on practice

- Tocilizumab as first or subsequent line is expected to provide an effective treatment for moderate to severe active and progressive rheumatoid arthritis.
- Tocilizumab is expected to prove to be very valuable in improving the function and quality of life and decreases fatigue, in subjects with rheumatoid arthritis.
- Short- and long-term use of Tocilizumab is expected to prove to be safe (trials on incidence of infections and cardiovascular adverse outcome data) in subjects with rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is associated with significant morbidity and mortality [1]. The available therapeutic options targeted chronic inflammatory conditions of diverse pathological responses. The current pharmacotherapeutic interventions for RA include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids (glucocorticoids), and disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX) / leflunomide and newer biologic DMARDs, the tissue necrosis factor (TNF-alfa) inhibitors biological agents such as infliximab [2], etanercept [3] Adalimumab [4], rituximab [5] and abacatum [6]. Interleukin-1 inhibitors (IL-1) such as anakinra [7], and the newly developed Interleukin-6 inhibitors (IL-6) tocilizumab and sarilumab, both targets IL-6 receptors [8].

The main goal of therapy for RA is to achieve clinical remission (treat-to-target paradigm) with no signs or symptoms or low disease activity with long-term outcome. The current management of RA is confronted with many challenges such as inadequate response and treatment failure. The cornerstone and first choice in RA therapy is MTX which is a conventional synthetic DMARD with broad immunosuppressive effects. However, in certain relevant patient conditions MTX will be combined with glucocorticoid therapy (short-term). One of the recent directed therapies is IL-6 inhibitors which have shown favorable results. The newly biologic agent Tocilizumab which inhibits interleukin-6 is approved for the treatment of RA. Tocilizumab has emerged as a novel interleukin-6 inhibitor that possesses some advantages over the other members of the class. It may offer advantage over conventional therapy for rheumatoid arthritis and may provide great opportunity to improves the control of rheumatoid arthritis (pain, stiffness and mobility) and prevent further progression of disability. Tocilizumab does not cause specific infection, while treatment with anti-TNF therapy has been associated with development of tuberculosis [9]. Tocilizum (8 mg/kg/month) was compared to etanercept (50 mg/week) in recent powered RCT (open-label – parallel group) in 3080 subjects with active seropositive RA (followed for mean of 3.2 years) for the development of major cardiovascular adverse events (MACE) as the primary end point. The estimated probability of events in tocilizumab compared to etanercept (hazard ratio) was 1.05 (95% confidence interval 0.77–1.43), which ruled out a risk for occurrence of MACE of 1.43 or higher in patients treated with tocilizumab [10].

Rationale of the systematic review

The current treatment options for RA are associated with high therapeutic failure rate which indicated the requirement for new interventions with improved efficacy. Therefore, therapy for subjects with RA deserves further exploration for optimum control of disability. The efficacy and safety profile of a newly class known as interleukin-6 inhibitor (tocilizumab) will assist to further optimize the management of RA. Tocilizumab is a novel IL-6 inhibitor that bears some potential in the management of RA.

In the current protocol, we intend to assess subjects (participants) with any type/stage of RA receiving tocilizumab (intervention) versus placebo or other anti-rheumatic drugs (comparators). The non-inferiority or superiority of tocilizumab will be appraised in terms of improving disease markers of disability (outcome). Furthermore, the safety profile for tocilizumab therapy will be assessed as compared to placebo/comparators. The differences aligned between tocilizumab and the other remedies will be reported based on the efficacy, precautions and safety profile and/or RA type.
**Aim and objective of the review**

We intend to assess the efficacy and safety of tocilizumab in subjects with RA using the data from published randomized controlled trials (RCTs). The aim of the current systematic review and meta-analysis is to explore the pros and cons of tocilizumab as a novel interleukin-6 inhibitor in terms of efficacy and safety that delineate its clinical utility in terms of improving RA management. The main objective of the current systematic review and meta-analysis will be to assess the efficacy and safety of tocilizumab in subjects with RA using the available evidence from published RCTs.

**Ethics approval**

Ethics approval is not requiring in the current systematic review and meta-analysis.

**METHODS**

We have followed the Cochrane library instructions in developing the current protocol for systematic review and meta-analysis on the efficacy and safety profiles of tocilizumab. The primary end-points will be the clinical responses and treatment improvements measured at the end of intent-to-treat (ITT) using any of the followings: the disease activity according to the American College of Rheumatology (ACR) criteria (ACR20/50/70/90), the Disease Activity Score in 28 joints (DAS28) remission responses and meaningful decrease in Health Assessment Questionnaire and modifies versions (HAQ/mHAQ).

The current protocol was registered on PROSPERO (Unique ID number CRD42020191568) and is available in full on the official PROSPERO website, [https://www.crd.york.ac.uk/PROSPERO/](https://www.crd.york.ac.uk/PROSPERO/). The developed protocol was based on the PRISMA-P checklist [http://www.prisma statement.org/Extensions/Protocols.aspx](http://www.prisma statement.org/Extensions/Protocols.aspx).

**Eligibility criteria**

We will conduct a systematic review and meta-analysis (participants, interventions, comparisons and outcomes [PICO], Figure 1) on phase II and phase III RCT-s for subjects with RA who have had received tocilizumab.

**Figure 1: Characteristics of included articles (PICO)**

**Method:** Randomized controlled trial with placebo and/or active comparator

**Participants:** Subjects with or without rheumatoid arthritis; population size and the number of randomized subjects in each arm of the trial; proportion of males versus females; age range (mean ± SD); BMI (mean ± SD); and relevant baseline clinical characteristics of subjects recruited.

**Interventions** tocilizumab (different doing) versus the comparator (doses of other comparators (Comparators) like methotrexate, Prednisone, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide).

**Outcomes:**

1. The primary outcome measure will be the clinical improvement in disability ACR20, ACR50, ACR70 and/or ACR 90 at the end of treatment in the ITT population.
2. The differences in treatment (effect size) between the intervention drug (tocilizumab) and placebo/comparators (methotrexate, prednisone) as non-inferiority or superiority will be reported.
3. The measures of effect will be improvement ACR20, ACR 50, ACR 70, DAS28, EULAR, ESR and/or minimization of adverse effects, from baseline to end-point of the trial.
4. Secondary outcomes: treatment emergent adverse events like cardiovascular events, hepatic events, decreasing disease activity in RA, inhibit the development of joint erosions, reduces the severity of inflammation, blood cholesterol disorders (due to which some patients have discontinued the treatment and/or withdrawn from the trial).

**Key words:** -Efficacy, interleukin-6 inhibitor, meta-analysis; randomized clinical trials; safety; systematic review; tocilizumab

The **inclusion criteria** will be the following: subjects diagnosed with RA (all forms), adult ≥18 years, both gender, hospitalized and non-hospitalized, subjects receiving intervention drug (tocilizumab) with placebo/comparator, RCT design (phase II RCT or phase III RCT,) trials published in English language, full text, primary outcome reported status of disability, the disease activity according to the American College of Rheumatology (ACR) criteria (ACR20/50/70/90), the Disease Activity Score in 28 joints (DAS28) remission responses and meaningful decrease in Health Assessment Questionnaire and modifies versions (HAQ/mHAQ) conducted on humans within the last years (2002 -2016).

The **exclusion criteria** will be non RCT, quasi experiment, trials with primary outcome other than the efficacy of tocilizumab, RCT with post-analysis studies, dose-finding RCT-s, retrospective trials, trial on pediatric population, and trials that have been conducted on pregnant and transplant subjects, and also exclude not full text, healthy subjects, extension trials, not RCTs, animal studies and nong-English language. The **types of studies** will be collected via conducting the search on the Google Scholar, Cochrane library, PubMed (NCBI/NLM), and EMBASE for published RCT in English language reporting the efficacy and safety of tocilizumab. We will conduct the search for published RCT (full text) on the English language reporting...
the efficacy and safety of tocilizumab. The current systematic review will be on RCTs phase II and phase III subjects. The setting will be out/in patients (hospitalized or not hospitalized). Trials will be retrieved during the period from the year 2002 to the year 2016.

**Types of participants, interventions, comparisons and outcomes**

Subjects diagnosed with RA (active/inactive) any type and receiving tocilizumab compared to placebo/comparators. The primary efficacy endpoint will be treatment improvement in disease activity according to the ACR criteria an ACR20 response, an ACR50 response, an ACR70 response, and an ACR90 response and DAS28 remission responses.

**Outcome measures**

The primary outcome measure will be the clinical responses and treatment improvement measured using the disease activity according to the American College of Rheumatology (ACR) criteria (ACR20/50/70/90), the Disease Activity Score in 28 joints (DAS28) remission responses and meaningful decrease in Health Assessment Questionnaire (HAQ/mHAQ) at the end of ITT. The differences in treatment between the intervention drugs and placebo/comparators as non-inferiority or superiority will be reported.

**The primary outcome measures are defined as:**

1. The major efficacy outcome (binary): ACR20, ACR50, ACR70 and/or ACR 90 defined as 20%, 50%, 70% and 90% improvement in both tender and swollen joint counts and any improvement in one of the following variables: patient’s global assessment, physician’s global assessment, pain scores, Health Assessment Questionnaire (HAQ) score and acute phase reactants (Erythrocyte Sedimentation Rate (ESR) or C-Reactive Protein (CRP), [11,12].
2. Safety: will be assessed by the number and type of adverse events (AEs) and serious adverse events (SAEs), withdrawals due to lack of efficacy, withdrawals due to adverse events, overall withdrawals and death.

The secondary safety endpoint will be the development of adverse events. The *measure of effect* will be expressed as relative risks, odds ratios, risk difference, and/or 'number needed to treat.'

**Search methods**

The search methods for trials retrieved will be conducted via Google Scholar, PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) for published RCTs involving subjects with RA receiving tocilizumab versus placebo or comparators. The database will be retrieved between the years 2002 to 2016 with the Medical Subject Headings (MeSH) search terms: rheumatoid arthritis (RA); “interleukin-6 inhibitor” (IL-6); “tocilizumab”; “randomized clinical trials”, “placebo”; “comparator”; “safety”; “efficacy”, which is shown as images in the supplementary material.

The **selection criteria will be** tocilizumab alone or in combination with disease-modifying anti-rheumatic drugs (DMARDs) or biologics compared to placebo or other DMARDs or biologics. The selected trials citations will be imported into systematic review managers/software (COVIDENCE https://www.covidence.org/ or RAYYAN https://rayyan.qcri.org/welcome). In addition, we will use the manual searched citations with the same MeSH terms and conditions.

**Search method for identification**

Medline in addition to Google Scholar, PubMed, by using the predefined Cochrane library approved structured modified forms. The relevant datasets will be collated by using the predefined Cochrane library approved structured modified forms. The draft of the search strategy to be used for one electronic database including planned limits was shown in, [diagram flow chart, Figure 2].

---

**Protocol for systematic review and meta-analysis on randomized clinical trials (placebo-controlled or comparator) on the efficacy and safety of tocilizumab interleukin (IL)-6 inhibitor in subjects with rheumatoid arthritis**

---

**Review question search:**

1. Does the interleukin-6 receptor modulators (tocilizumab) prove superiority over placebo or comparators in subjects with RA?

2. Does tocilizumab demonstrate a better safety profile as compared to other drug classes used in RA?

---

**Articles were excluded:**

- Non RCT, quasi experiment
- Trial on pediatric population
- Trials that have been conducted on pregnant and transplant subjects
- Trials with primary outcome
- RCT with post-analysis studies
- Retrospective trials
- Non-English Language
- Not full text
- Healthy subjects
- Extension trials
- Animal studies

**Limits of search used**

Year 2002 - 2019

---

**Mesh Term:**

Tocilizumab, 2002-2016, RA, RCT, adult, placebo, comparator, ACR20, ACR50, ACR70, ITT

---

**Google Scholar** search yielded... Articles

**PubMed** yielded... EMBASE yielded... (2002-2016)

**[Checked for duplication]**... articles *excluded*
**Number of articles**... excluded with reasons.

**References:**

[Numerous references are listed here, indicating detailed studies and data sources.]

---

**Nine articles were screened for the below-mentioned inclusion criteria (initial screening):**

1. Trials published in English Language
2. Human research
3. Within the last 18 years (2002-2016)
4. Multiple sclerosis
5. Adult ≥ 18 years
6. RCT's with comparator
7. Hospitalized and non-hospitalized
8. Rheumatoid arthritis
9. Tocilizumab

---

**Nine articles were finally included:**

The final retrieved article which has met the above-mentioned inclusion criteria are ... RCT's (2002-2016) A systematic review and meta-analysis on randomized clinical trials (placebo-controlled or comparator) on the efficacy and safety of tocilizumab interleukin (IL)-6 inhibitor in subjects with rheumatoid arthritis

**References:**

[Numerous citations are provided, linking back to the original studies and articles.]
RCTs and supplementary materials. Data extraction (selection and coding) will be performed on the relevant variables from the original RCT and supplementary materials. The data extraction will contain trial registration, study country, number of involved countries (trial centers), type of RA, stage of RA, trial duration, follow-up duration, withdrawal, the efficacy data, primary endpoint (outcomes measures), the safety outcomes (adverse events) for the included trials. The above data will be collated with structured forms, verified, reviewed, double checked, and recorded in final format in (Cochrane templates) and will be transferred into the RevMan 5.4 database.

Data items

Data items will be defined for all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications. PICO items: we will conduct a systematic review and meta-analysis (participants, interventions, comparisons and outcomes [PICO]) on phase II and phase III RCT-s for subjects with RA who have received tocilizumab. Subjects both gender with any type of RA (participants) and receiving tocilizumab (intervention) for management of RA randomized versus placebo or comparator (comparison). The primary efficacy endpoint will be ACR20, ACR50, ACR70 and/or ACR 90 defined as 20%, 50%, 70% and 90% improvement in both tender and swollen joint counts and any improvement in one of the following variables: patient’s global assessment, physician’s global assessment, pain scores, Health Assessment Questionnaire (HAQ) score and acute phase reactants (Erythrocyte Sedimentation Rate [ESR] or C-Reactive Protein [CRP] and/or their composite (outcomes).

Outcome measures

The primary outcome measure will be the clinical improvement in ACR20, ACR50, ACR70 and/or ACR 90 at the end of treatment in the ITT population. The differences in treatment (effect size) between the intervention drug (tocilizumab) and placebo/comparators (e.g. methotrexate) as non-inferiority or superiority will be reported. The measures of effect will be the improvement in ACR20, ACR50, ACR70 and/or ACR 90. The magnitude of differences between tocilizumab and the placebo or the comparator will be of high priority.

The risk of bias in individual studies (quality of RCT-s and assessment of risk of bias)

The quality of the RCT-s (both at study level and outcome) will be assessed with a five-point scale to minimize and avoid bias in the inclusion of relevant RCT-s [14]. The method that will be followed as per the risk of bias tool, version 2.0 (Cochrane) will be used for the risk of bias assessment.

Data Synthesis

The data synthesis (quantitative, qualitative, descriptive, inferential statistics and meta-analysis) will be performed. The quantitative synthesis for the variation in effects (clinical heterogeneity) in the RCT-s included in the current systematic review and meta-analysis will be at all levels of trials (relevant population level, the intervention level, outcomes level (ITT: clinical success, superiority/inferiority and statistical magnitude of difference) and planned summary measure. The RevMan version 5.4 will be used for meta-analyses (with consistency) to combine and explore data from respective trials. The clinical outcomes will be assessed with the random effects model (e.g. I² index, tau squared, and the Q-test P value, meta-regression for heterogeneity) with the Mantel-Haenszel (MH) method (pooled estimates of odds ratio (OR) with 95% confidence interval [CI]), independent pooling of data to reduce the risk of bias, and funnel plots and Egger’s linear regression test of funnel plot asymmetry to assess the publication bias. Other measures that will be used such as sensitivity analysis to reveal inconsistency and forest plots to show the relative effect size of the intervening comparator for each clinical endpoint (pre-specified and expected outcomes free of selective reporting).

Data Synthesis

The purpose of this systematic review and meta-analysis is to assess the efficacy and safety of tocilizumab, compare and explore the efficacy and safety versus other comparators in terms of ACR scores. The data synthesis will be qualitative and descriptive data will be presented, and inferential statistics and meta-analysis will be performed.

Exploration of variation in effects

The variations of effects (heterogeneity) in the RCT-s included in the current systematic review and meta-analysis comprised a set of clinical covariates (clinical heterogeneity) from the relevant population level (matched groups of RA), the intervention level (intervention vs. comparator), outcomes level (ITT: clinical success and other relevant endpoints). Appropriate data for quantitative synthesis, will be reported as planned summary measures (handling and combining data from studies), including exploration of consistency (e.g., I2, Kendall’s tau).

The proposed additional analyses: we will conduct meta-analysis in the current systematic review as well as reporting the sensitivity analysis. We also plan a structured synthesis of data and comparison between the inferences in the respective trials (e.g., sensitivity and/or subgroup analyses and/or meta-regression). Data will be pooled using random-effects models. The proposed additional analyses will be structured synthesis of data and comparison between the inferences in the respective trials (e.g., sensitivity and/or subgroup analyses and/or meta-regression). Data will be pooled using random-effects models.

The meta-bias: The publication bias is defined as the failure to publish the results of a study on the basis of the direction or strength of the study findings. In the current systematic review and meta-analysis, we will use a funnel plot to check for the existence of publication bias or systematic heterogeneity in the studies taken for analysis. We will use Egger’s regression for quantifying funnel plot asymmetry or Rosenthal’s fail-safe number or “fail-safe N method”. We will plan to avoid selective reporting within trials by not excluding non-significant study outcomes and by describing structured search criteria based on published methodologies. Confidence in cumulative evidence: we will assess the strength of evidence of the final results in a GRADE Evidence Profile (GEP). This GEP will contain the PICO question, the type and number of trials included in the current systematic review and meta-analysis, the effect sizes and their confidence intervals and the grading of the quality of the evidence and its starting level and reasons for upgrading or downgrading the quality. The quality of evidence for all outcomes for the included trials will be judged using an adaptation of the GRADE methodology assessment, [15-17] and will be assessed crosswise the domains of risk of bias (consistency, directness, precision and publication bias). The full electronic search strategy in the database, limits of search used, check of duplication as per the PRISMA guidelines,
will be shown in; [Figure-diagram 2]. The PRISMA chart and the complete PRISMA-P form will be provided in the supplementary material, Appendix I.

**PRISMA-P 2015 Checklist**

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

<table>
<thead>
<tr>
<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
<th>Information reported</th>
<th>Line number(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADMINISTRATIVE INFORMATION</strong></td>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Title</td>
<td>1a</td>
<td>Identify the report as a protocol of a systematic review</td>
<td>☒</td>
<td>☐</td>
</tr>
<tr>
<td>Update</td>
<td>1b</td>
<td>If the protocol is for an update of a previous systematic review, identify as such</td>
<td>☐</td>
<td>☒</td>
</tr>
<tr>
<td>Registration</td>
<td>2</td>
<td>If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract</td>
<td>☒</td>
<td>☐</td>
</tr>
<tr>
<td>Authors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact</td>
<td>3a</td>
<td>Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author</td>
<td>☒</td>
<td>☐</td>
</tr>
<tr>
<td>Contributions</td>
<td>3b</td>
<td>Describe contributions of protocol authors and identify the guarantor of the review</td>
<td>☒</td>
<td>☐</td>
</tr>
<tr>
<td>Amendments</td>
<td>4</td>
<td>If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments</td>
<td>☒</td>
<td>☐</td>
</tr>
<tr>
<td>Support</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sources</td>
<td>5a</td>
<td>Indicate sources of financial or other support for the review</td>
<td>☒</td>
<td>☐</td>
</tr>
<tr>
<td>Sponsor</td>
<td>5b</td>
<td>Provide name for the review funder and/or sponsor</td>
<td>☒</td>
<td>☐</td>
</tr>
<tr>
<td>Role of sponsor/funder</td>
<td>5c</td>
<td>Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol</td>
<td>☒</td>
<td>☐</td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>6</td>
<td>Describe the rationale for the review in the context of what is already known</td>
<td>☒</td>
<td>☐</td>
</tr>
<tr>
<td>Objectives</td>
<td>7</td>
<td>Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)</td>
<td>☒</td>
<td>☐</td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>8</td>
<td>Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review</td>
<td>☒</td>
<td>☐</td>
</tr>
<tr>
<td>Information sources</td>
<td>9</td>
<td>Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage</td>
<td>☒</td>
<td>☐</td>
</tr>
<tr>
<td>Search strategy</td>
<td>10</td>
<td>Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated</td>
<td>☒</td>
<td>☐</td>
</tr>
</tbody>
</table>
We will present the systematic review results and the meta-analysis results in complete tables based on PICO comparison between the included trials. The results will contain a systematic critical evaluation of the included RCTs in terms of the number of the population characteristics, the dosing of intervention (tocilizumab) and the comparators, the main outcome measures. The necessary elements of PRISMA will be strictly followed to report the systematic review. The meta-analysis will be reported with the Cochrane guidelines in synthesis of RCTs and all forms will be based on the quality measures as per the validated Cochrane templates. The pharmacological characteristics of two congers of interleukin-6 inhibitor were shown in [Table 1].
### Table 1. Comparison of the pharmacological characteristics of IL-6 receptor antagonist used for rheumatoid arthritis

<table>
<thead>
<tr>
<th>IL-6 Trademark (proprietary name)</th>
<th>Tocilizumab</th>
<th>Sarilumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>- Tocilizumab is an IL-6 receptor inhibitor that binds specifically to both the soluble and membrane-bound IL-6 receptors and has been shown to inhibit IL-6 mediated signaling via these receptors.</td>
<td>- Sarilumab inhibits IL-6 mediated signaling by binding to IL-6 receptors that are both soluble and membrane-bound.</td>
</tr>
</tbody>
</table>
| **Approved**                     | - RA (moderate to severe)  
- May be used as monotherapy or in combination with methotrexate (MTX) or other conventional DMARDs  
- Juvenile RA - Systemic onset juvenile chronic arthritis  
- Cytokine release syndrome - Temporal arteritis | - RA (moderate to severe)  
- May be used as monotherapy or in combination with methotrexate (MTX) or other conventional DMARDs |
| **Indications**                  | - RA, giant cell arthritis  
- Polyarticular juvenile idiopathic arthritis  
- Systemic juvenile idiopathic arthritis and cytokine release syndrome in both adults and children  
- COVID-19 | - RA (moderate to severe)  
- COVID-19 (not FDA approved), used with the investigation protocol. |
| **Adult dosing**                 | - RA (moderate to severe):  
- 4 mg/kg IV infusion over 1 hour every 4 weeks; increase to 8 mg/kg every 4 weeks based on clinical response; doses exceeding 800 mg per infusion are not recommended  
- available as prefilled syringe and prefilled pen  
- The prefilled syringe is a single-dose needle that is manually injected.  
- The ACTPen auto-injector is a prefilled, single-dose, pen-like auto-injector that keeps the needle tip shielded before the injection, allowing you to inject by holding down a button. | - RA (moderate to severe):  
- 200 mg subQ once every 2 weeks  
- available as prefilled syringe and prefilled pen |

Cont. Table 1. Comparison of the pharmacological characteristics of IL-6 receptor antagonist used for rheumatoid arthritis

<table>
<thead>
<tr>
<th>IL-6 Trademark (proprietary name)</th>
<th>Tocilizumab</th>
<th>Sarilumab</th>
</tr>
</thead>
</table>
| **Route of administration**      | - SC  
- IV route for the treatment of cytokine release syndrome | -SC |
| **Bioavailability**              | - Bioavailability, subQ: 80% (RA) | - Tmax, subQ: 2 to 4 days |
| **Peak concentration**           | - Vd, polyarticular juvenile idiopathic arthritis: 4.08 L | - Vd: 7.3 L |
| **Volume of distribution**       | - Total body clearance, RA: 12.5 mL/hr, 216 mL/day | - |
| **Total body clearance**         | - Rheumatoid arthritis: up to 11 days (multiple-dose, 4 mg/kg IV);  
up to 13 days (multiple-dose, 8 mg/kg IV);  
up to 13 days (multiple-dose, 162 mg subQ every week);  
up to 5 days (multiple-dose, 162 mg subQ every other week) | -2 to 4 days |
| **Elimination half-life**        | - Monitor neutrophil counts and platelets  
- Monitor ALT and AST levels  
- liver function tests (ie, bilirubin)  
- Assess lipid parameters  
- Test for latent TB prior to initiation, monitor all patients for active TB during treatment | -Monitor neutrophil counts and platelets  
- Monitor ALT and AST levels  
- liver function tests (ie, bilirubin)  
- Assess lipid parameters |
| **Monitoring**                   | | |
Monitor patient closely for signs and symptoms of infection during and after therapy

- Test for latent TB prior to initiation, monitor all patients for active TB during treatment
- Monitor patient closely for signs and symptoms of infection during and after therapy

**Cont. Table 1. Comparison of Pharmacological Characteristics of IL-6 Receptor Antagonist Used for Rheumatoid Arthritis**

<table>
<thead>
<tr>
<th>IL-6 Trademark (proprietary name)</th>
<th>Tocilizumab</th>
<th>Sarilumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contraindications</strong></td>
<td>- Hypersensitivity to tocilizumab</td>
<td>- Hypersensitivity to sarilumab or excipients</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>- Live vaccines: concurrent use of tocilizumab and live vaccines may result in reduced effectiveness of immunization. - Potent immunosuppressants: concurrent use of tofacitinib and potent immunosuppressants may result in increased risk of immunosuppression. - Infliximab: concurrent use of infliximab and tocilizumab may result in increased immunosuppression and an increased risk of infections.</td>
<td>- Infliximab and biologic agents: concurrent use of infliximab and biologic agents may result in increased immunosuppression and an increased risk of infections. - Live vaccines: concurrent use of sarilumab and live vaccines may result in an increased risk of infections caused by the live or attenuated vaccine.</td>
</tr>
<tr>
<td><strong>Pregnancy and lactation</strong></td>
<td>- Pregnancy: fetal risk cannot be ruled out - Breast feeding: infant risk cannot be ruled out</td>
<td>- Pregnancy: teratogenicity effects and fetal risk cannot be ruled out - Breastfeeding: Infant risk cannot be ruled out</td>
</tr>
</tbody>
</table>

**Cont. Table 1. Comparison of Pharmacological Characteristics of IL-6 (IL-6) Receptor Antagonist Used for Rheumatoid Arthritis**

<table>
<thead>
<tr>
<th>IL-6 Trademark (proprietary name)</th>
<th>Tocilizumab</th>
<th>Sarilumab</th>
</tr>
</thead>
</table>

**Key:** ALT: Alanine aminotransferase, SGPT: Serum glutamic pyruvic transaminase, AST: Aspartate aminotransferase, COVID-19: Coronavirus, IL-6: Interleukin-6, IV: Intravenous, RA: Rheumatoid arthritis, C: Subcutaneous route, Tmax: Time of Maximum concentration observed, TB: Tuberculosis, Vd: Volume of Distribution
DISCUSSION
The role of IL-6 inhibitors has evolved in the last recent years with successful remissions and improved clinical outcomes. Hence, our current systematic review and meta-analysis will provide highly relevant findings of evidence for the role of IL-6 inhibitor (tocilizumab) in the management of RA, [18-27]. This will permit the prescribers to make informed decisions about the most efficacious and safest regimen for their clients. The findings of the current systematic review and meta-analysis will contribute to inform evidence-based clinical practices and add to the gained knowledge of such therapy. Furthermore, the findings will help to inform researcher and expand the future subsequent research, and evaluation of additional population interventions. The work will provide evidence by synthesis of well-designed and robust RCTs conducted on one of the most efficacious and safest interleukin-6 inhibitors. We intend to minimize the publication bias and reporting bias with the use of published technical methods as mentioned previously in the protocol. We intend to share our findings with the academia and rheumatology societies worldwide. The main objectives in the management of RA are to control synovitis, prevent joint injury and promote the quality of life of affected subjects. The goal is to achieve early, rapid and sustained remission and/or minimize the diseases activity by the most efficacious and safest regimens. Therefore, the choice of therapy (from DMARD) should be based on recent evidence from RCT and relevant expert opinions. Several factors contribute to achieving the outset goals, such as the patient’s response, the severity of the disease’s activity, the status of the initiated regimen/prior treatment and the emergence of resistant situations. The management of RA continues to be confronted with treatment failure, suboptimal management and emergence of resistant to certain regimens. The decision on which therapy to be used in the management of RA, is challenged with subjects’ preferences. Recent data has supported shared decision-making between physicians and their patients on the use of tocilizumab [28]. A systematic review of 36 studies has summarized patients’ preferences for disease modifying anti-rheumatic drug (DMARD) therapy in RA. The risk-benefit concept needed to take into consideration the patient preferences in decision-making (such as treatment benefit, willingness to accept cost and risk), which dictate the individualized treatment approach. [29]

FUNDING
We declare no special funding was obtained.

CONFLICT OF INTEREST
The authors would like to acknowledge no conflict of interest.

ACKNOWLEDGEMENT
We would like to acknowledge the efforts of Dr Israa and Dr Doaa, for their dedicated work in leading the current research group.

REFERENCES


