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

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ABSTRACT

Background: Tocilizumab is a novel interleukin-6 inhibitor that possesses some advantages over the other members of the class and over conventional therapy for rheumatoid arthritis.

Aim of the review: The aim of the current protocol for the systematic review and meta-analysis is to assess the efficacy and safety of tocilizumab.

Methods: The protocol has been developed based on the PRISMA-P checklist by using (PICO [population, intervention, comparators, and outcome]) items, for adult subjects who have received tocilizumab in randomized clinical trials. We will search Google Scholar, PubMed, and the Cochrane Central Register for randomized controlled clinical trials using specific MESH terms. The subjects with rheumatoid arthritis (population) receiving tocilizumab (intervention) will be compared to placebo or other interleukin-6 inhibitors (comparators), for the non-inferiority or superiority in terms of effects on disability and/or other disease clinical markers (outcome). The RevMan will be used to quantify the synthesis of data. Whereas I2 index, tau squared, and the Q-test P value will be used to examine heterogeneity among individual study effect sizes.

Anticipated results: 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 RCT-s 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 RCT-s and all forms will be based on the quality measures as per the validated Cochrane templates.

Conclusion: This protocol will report the differences in the efficacy and safety of tocilizumab (intervention) as compared to the placebo or other interleukin-6 inhibitors (comparators).

Keywords: Efficacy, interleukin-6 inhibitors (IL-6), meta-analysis; randomized clinical trials; safety; systematic review; tocilizumab

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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 pharmaco-therapeutic 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 abatacept [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]. Tocilizumb (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/# myprospero). The developed protocol was based on the PRISMA-P checklist 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.

- **The magnitude of difference between tocilizumab and the placebo or the comparator will be of high priority.**

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 non- 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

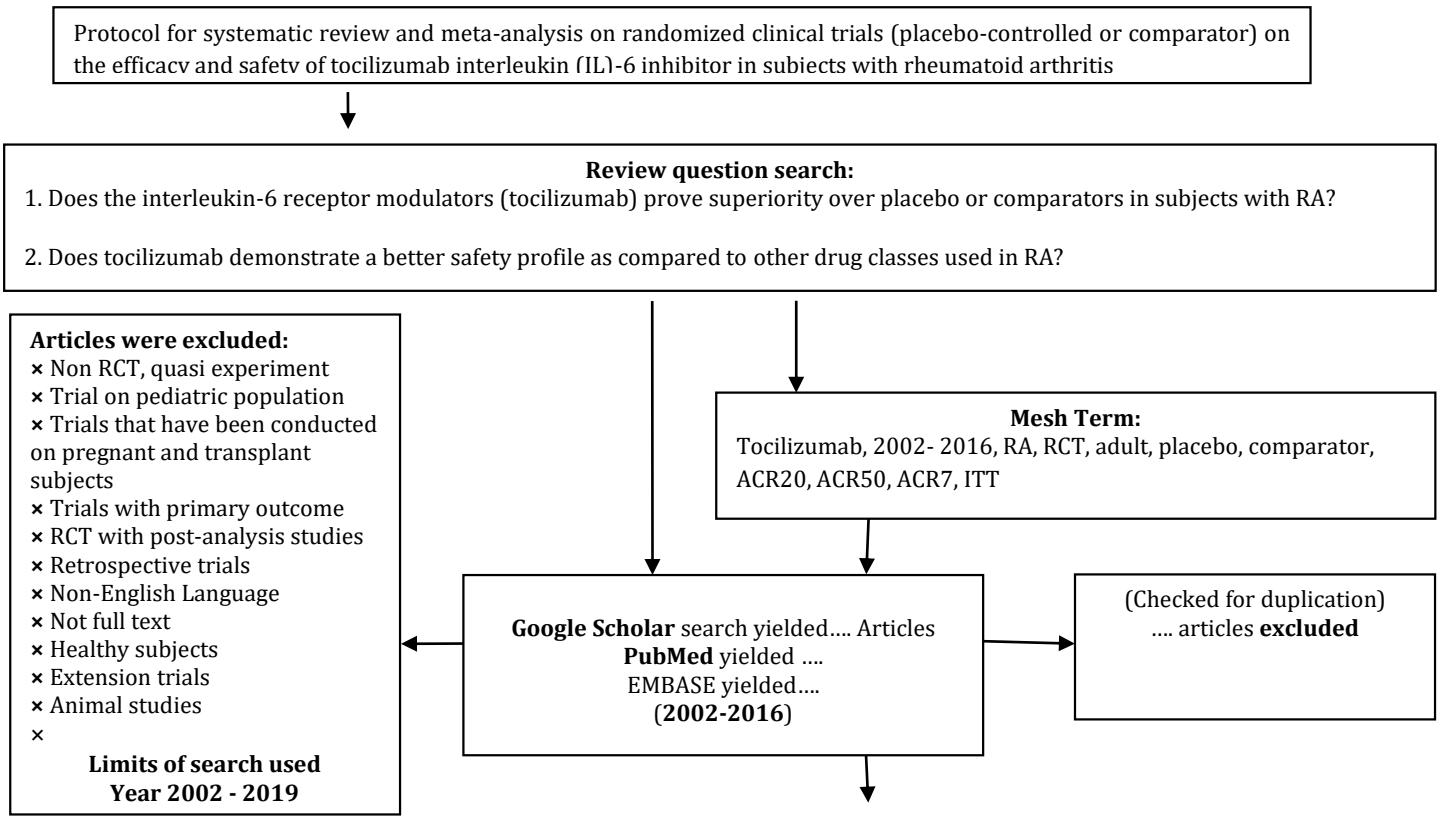
The **search methods** for trials retrieved will be conducted via Google Scholar, PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) for published RCTs involving subjects with RA receiving tocilizumab versus placebo or comparators. The database will be retrieved between 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**].



Number of articles……. excluded with reasons.

References:
[……..]

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: ……..

Keys:

ACR: American College of Rheumatology, **IL:** interleukin, **ITT:** Intent-to-treat, **RA:** Rheumatoid arthritis, **RCTs:** Randomized controlled trials

The trials information sources (data)

Study records

Data management

The collection of data and the data analysis will be via the access of full articles, screened and reviewed content with predefined checklist (Cochrane templates) developed and modified specifically to align with the strict inclusion criteria. We will follow the checklist that has been adapted for use with protocol submissions to Systematic Reviews from Moher [13].

Selection process

The selection process of the trials will be conducted by all the authors based on the inclusion and exclusion criteria. The methods will be used for identifying published trials in the official websites will be structured, predefined and specific MeSH terms for identifying eligible trials for inclusion in the current systematic review and meta-analysis. We will follow a strict checklist with pre-specified inclusion and exclusion criteria to ensure that the identified trials are as per the current systematic review and meta-analysis methodology. The authors (AS, A Sadeq, IK, DN, IMA, and JA) will double check the process and repeat the search terms individually and will compare the attempts, whereby, discrepancies will be resolved with discussions in reporting. The selected trials will be further reviewed by (JD, MEH, NA, SMM, NAK and HA), will be double checked by other different authors (WSME, EEGO, HSAA and HAA), and will be verified by repeating the process mentioned-above.

The final double checking and verification will ensure that the selected trials precisely met the final relevant information and primary outcome needed for the current systematic review and meta-analysis (SAAE, A Adel, ABA, AE, AAL, FHF, SMES and NAL). The type of RA, trial duration, follow-up duration and primary end point (outcomes measures) will be shown in the supplementary material. The trials registration, DOI, author details, and results of the outcome of the respective included RCT will be presented. The safety outcomes (AEs) for the trials included in the current systematic review will be presented in tables.

Data extraction and synthesis

The data extraction and synthesis will be via the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, which will be used to abstract data and assess quality and validity from original

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 difference 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 RCTs 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. I^2 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 RCTs 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 the number of participants in the trials, 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

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	-
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	205
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	15-74
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	75
Amendments	4	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	☒	☐	83
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	85
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	87
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	89
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	173
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	187
METHODS					
Eligibility criteria	8	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	☒	☐	209
Information sources	9	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	☒	☐	267
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	270

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	274
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	280
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	299
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	310
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	323
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	330
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	335
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	354
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	360-364
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	368
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	377

RESULTS

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 RCT-s 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 RCT-s 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

IL-6 Trademark (proprietary name)	**Tocilizumab**	**Sarilumab**
Mechanism of Action	- 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	- Sarilumab inhibits IL-6 mediated signaling by binding to IL-6 receptors that are both soluble and membrane-bound
Approved	- RA (moderate to severe) - May be used as monotherapy or in combination with methotrexate (MTX) or other conventional D MARDs - 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 arteritis - 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

IL-6 Trademark (proprietary name)	**Tocilizumab**	**Sarilumab**
Rote of administration	- SC - IV route for the treatment of cytokine release syndrome	-SC
Bioavailability **Peak concentration**	- Bioavailability, subQ: 80% (RA)	- Tmax, subQ: 2 to 4 days
Volume of distribution	- Vd, polyarticular juvenile idiopathic arthritis: 4.08 L	-Vd: 7.3 L
Total body clearance	- Total body clearance, RA: 12.5 mL/hr, 216 mL/day	-
Elimination half-life	- 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
Monitoring	- 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

	- 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 the pharmacological characteristics of IL-6 receptor antagonist used for rheumatoid arthritis

IL-6 Trademark (proprietary name)	**Tocilizumab**	**Sarilumab**
Contraindications	- Hypersensitivity to tocilizumab	- Hypersensitivity to sarilumab or excipients
Interactions	- 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.	- 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 caused by the live or attenuated vaccine.
Pregnancy and lactation	- Pregnancy: fetal risk cannot be ruled out - breast feeding: infant risk cannot be ruled out	- Pregnancy: teratogenicity effects and fetal risk cannot be ruled out - Breastfeeding: Infant risk cannot be ruled out

Cont. Table 1. Comparison of Pharmacological Characteristics Interleukin-6 (IL-6) receptor antagonist used for rheumatoid Arthritis

IL-6 Trademark (proprietary name)	**Tocilizumab**	**Sarilumab**
Main adverse drug reactions	**Common**: - - **Cardiovascular**: hypertension **- Dermatologic**: injection site reaction **- Gastrointestinal**: diarrhea, upper abdominal pain **- Hepatic**: ALT/SGPT level raised, aspartate aminotransferase serum level raised **- Neurologic**: dizziness, Headache **- Respiratory**: nasopharyngitis **Serious**: - **-Gastrointestinal:** gastrointestinal perforation, pancreatitis **- Hematologic**: decreased platelet count, neutropenia - **Hepatic**: hepatotoxicity **- Immunologic**: anaphylaxis, hypersensitivity reaction, opportunistic infection, tuberculosis **- Respiratory**: upper respiratory infection	**Common**: - **- Dermatologic**: erythema at injection site, Injection site reaction **- Hematologic**: neutropenia **- Hepatic**: ALT/SGPT level raised **- Renal**: urinary tract infectious disease **Serious**: - **- Gastrointestinal**: gastrointestinal perforation **- Immunologic**: herpes zoster **- Respiratory**: tuberculosis

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 RCT-s 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 safety 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]

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CONFLICT OF INTEREST

The authors would like to acknowledge no conflict of interest.

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