# DAFTAR PUSTAKA


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# LAMPIRAN 1

# PROTOKOL PROSPERO

**PROSPERO**
**International prospective register of systematic reviews**

NHS
National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

## Systematic review

*Fields that have an **asterisk (*)** next to them means that they **must be answered. Word limits** are provided for each section. You will be unable to submit the form if the word limits are exceeded for any section. Registrant means the person filling out the form.*

This record cannot be edited because it has been marked as out of scope

### 2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

Efektivitas dan Keamanan Baricitinib Sebagai Kandidat Obat COVID-19: Sebuah Kajian Sistematik

### 3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

01/03/2021

### 4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

28/02/2022

### 5. * Stage of review at time of this submission.

**This field uses answers to initial screening questions. It cannot be edited until after registration.**

Tick the boxes to show which review tasks have been started and which have been completed.

Update this field each time any amendments are made to a published record.

The review has not yet started: No

| Review stage | Started | Completed |
|---|---|---|
| Preliminary searches | Yes | Yes |
| Piloting of the study selection process | Yes | Yes |
| Formal screening of search results against eligibility criteria | Yes | Yes |
| Data extraction | Yes | Yes |
| Risk of bias (quality) assessment | Yes | Yes |

| Review stage | Started | Completed |
|---|---|---|
| Data analysis | Yes | Yes |

Provide any other relevant information about the stage of the review here.

## 7. * Named contact email.

Give the electronic email address of the named contact.

yayuksrirahay05@gmail.com

## 9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+62 8114090027

## 11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Mrs Yayuk Sri Rahayu. Hasanuddin University, Makassar City, South Sulawesi Province, Indonesia, 90245
Ms A. Anggriani. Hasanudddin University, Makassar, Indonesia
Mr Habibie Habibie. University Of Groningen, Groningen, The Netherlands
Mr Muh. Akbar Bahar. Hasanuddin University, Makassar, Indonesia
Mrs Elly Wahyudin. Hasanuddin University, Makassar, Indonesia

## 13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

## 14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

## 16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

("COVID-19" [Supplementary Concept]) OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept]) OR "Severe Acute Respiratory Syndrome"[MeSH]) OR (SARSCoV-2[tiab] OR COVID-19[tiab] OR2019 nCOV[tiab] OR COVID19[tiab] OR "severe acute respiratory syndrome coronavirus 2"[tiab] OR "2019 novel coronavirus disease"[tiab] OR "COVID-19 pandemic"[tiab] OR "SARS-CoV-2 infection"[tiab] OR "COVID-19 virus disease"[tiab] OR "2019 novel coronavirus infection"[tiab] OR "2019-nCoV infection"[tiab] OR "coronavirus disease 2019"[tiab] OR "coronavirus disease-19"[tiab] OR "2019-nCoV disease"[tiab] AND (("Baricitinib" [Supplementary

## 18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic

review.

At the beginning of 2020, the world was shocked by the outbreak of a new virus, namely the new type of corona virus (SARS-CoV-2) and the disease is called Coronavirus Disease-2019. It is known that the origin of this virus came from Wuhan, China. On March 11, 2020, WHO declared COVID-19 a pandemic disease. The presence of a hyper-inflammatory response characterized by cytokine storm syndrome is thought to cause the infected patient to suddenly worsen and develop acute respiratory distress syndrome to shock. Baricitinitib is expected to be a drug that can block cytokine storms by suppressing JAK1 / JAK2. To support the use of Baricitinib as an alternative drugs for COVID-19, we need to perform a systematic review to evaluate the effectiveness and safety of this drug on COVID-19 patients.

## 20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Baricitinib in the treatment of Covid-19

## 22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

All experimental, observational studies or case reports / case series that report the effectiveness and/or the safety of Baricitinib in patients infected with Covid-19 with mild, moderate to severe severity.

## 24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Effectiveness of baricittinib is characterized by clinical improvement, reduced risk of ICU admission and reduced risk of death

Any outcomes (RR, OR, RD, NNT) reported by the articles

## 26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Records resulted from databases searching will be screened based on inclusion and exclusion criteria. Title and abstract screening will be conducted by two review authors independently. Full-text report of peer-reviewed studies which have passed from title and abstract screening will be screened further by two review authors independently for final decision of studies eligibility. Authors of original studies will be contacted by email if clarification regarding studies eligibility is needed. Disagreement between review authors regarding studies eligibility will be resolved through discussion.Results selected: study design, baricitinib dose, study population, efficacy and safety, side effects, severity, cure rate, mortality rate and duration of drug

administration.

## 28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This but should be and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

Data from eligible studies which are sufficient and homogenous will be included in a meta-analysis using a random effect model with Review Manager (RevMan) by the Cochrane Collaboration. If the data are not homogenous enough, it will be presented descriptively.

## 30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

### Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Living systematic review
No

Meta-analysis
No

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
Yes

For COVID-19 registrations please tick all categories that apply. Doing so will enable your record to appear in area-specific searches

Chinese medicine
Diagnosis
Epidemiological
Genetics
Health impacts
Immunity
Long COVID
Mental health
PPE
Prognosis
Public health intervention
Rehabilitation
Service delivery
Transmission
Treatments
Vaccines
Other

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
Yes

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation

No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

## 32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

## 34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

**No I do not make this file publicly available until the review is complete**

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

## 36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Baricitinib; COVID-19

## 37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.
Please provide anticipated publication date

Review_Ongoing

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

## LAMPIRAN 2

## TABEL HASIL TELAAH KRITIS ARTIKEL

**1. Combined intravenous immunoglobulin and baricitinib treatment for severe COVID-19 with rhabdomyolysis: A case report.**

| No | | Yes | No | Unclear | Not applicable |
|---|---|---|---|---|---|
| 1. | Were patient's demographic characteristics clearly described? | ✔ | | | |
| 2. | Was the patient's history clearly described and presented as a timeline? | ✔ | | | |
| 3. | Was the current clinical condition of the patient on presentation clearly described? | ✔ | | | |
| 4. | Were diagnostic tests or assessment methods and the results clearly described? | ✔ | | | |
| 5. | Was the intervention(s) or treatment procedure(s) clearly described? | ✔ | | | |
| 6. | Was the post-intervention clinical condition clearly described? | ✔ | | | |
| 7. | Were adverse events (harms) or unanticipated events identified and described? | ✔ | | | |
| 8. | Does the case report provide takeaway lessons? | ✔ | | | |

**2. Attenuation of COVID-19-induced cytokine storm in a young male patient with severe respiratory and neurological symptoms.**

| NO | | Yes | No | Unclear | Not applicable |
|---|---|---|---|---|---|
| 1. | Were patient's demographic characteristics clearly described? | ✔ | | | |
| 2. | Was the patient's history clearly described and presented as a timeline? | ✔ | | | |
| 3. | Was the current clinical condition of the patient on presentation clearly described? | ✔ | | | |
| 4. | Were diagnostic tests or assessment methods and the results clearly described? | ✔ | | | |
| 5. | Was the intervention(s) or treatment procedure(s) clearly described? | ✔ | | | |
| 6. | Was the post-intervention clinical condition clearly described? | ✔ | | | |
| 7. | Were adverse events (harms) or unanticipated events identified and described? | ✔ | | | |
| 8. | Does the case report provide takeaway lessons? | ✔ | | | |

**3. Baricitinib as rescue therapy in a patient with COVID-19 with no complete response to sarilumab**

| NO | | Yes | No | Unclear | Not applicable |
|---|---|---|---|---|---|
| 1. | Were patient's demographic characteristics clearly described? | ✔ | | | |
| 2. | Was the patient's history clearly described and presented as a timeline? | ✔ | | | |
| 3. | Was the current clinical condition of the patient on presentation clearly described? | ✔ | | | |
| 4. | Were diagnostic tests or assessment methods and the results clearly described? | ✔ | | | |
| 5. | Was the intervention(s) or treatment procedure(s) clearly described? | ✔ | | | |
| 6. | Was the post-intervention clinical condition clearly described? | ✔ | | | |
| 7. | Were adverse events (harms) or unanticipated events identified and described? | ✔ | | | |
| 8. | Does the case report provide takeaway lessons? | ✔ | | | |

**4. Additional baricitinib loading dose improves clinical outcome in COVID-19**

| No | | Yes | No | Unclear | NA |
|---|---|---|---|---|---|
| 1. | Was true randomization used for assignment of participants to treatment groups? | ✔ | | | |
| 2. | Was allocation to treatment groups concealed? | | | ✔ | |
| 3. | Were treatment groups similar at the baseline? | ✔ | | | |
| 4. | Were participants blind to treatment assignment? | | | ✔ | |
| 5. | Were those delivering treatment blind to treatment assignment? | | | ✔ | |
| 6. | Were outcomes assessors blind to treatment assignment? | | | ✔ | |
| 7. | Were treatment groups treated identically other than the intervention of interest? | ✔ | | | |
| 8. | Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? | ✔ | | | |
| 9. | Were participants analyzed in the groups to which they were randomized? | ✔ | | | |
| 10. | Were outcomes measured in the same way for treatment groups? | ✔ | | | |
| 11. | Were outcomes measured in a reliable way? | ✔ | | | |
| 12. | Was appropriate statistical analysis used? | ✔ | | | |
| 13. | Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and | ✔ | | | |

**5. Experience with the use of baricitinib and tocilizumab monotherapy or combined, in patients with interstitial pneumonia secondary to coronavirus COVID-19: a real-word study**

| Citation: Rosas, 2020<br>*Are there other companion papers from the same study?* | |
|---|---|
| | Yes/ Can't tell/ No |
| 1. Is the study design clearly stated? | Yes |
| 2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Outcomes. | Yes |
| 3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; data collection. | Yes |
| 4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants. | Yes |
| 5. Are participant characteristics provided? Consider if: sufficient details; a table is included. | Yes |
| 6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable. | Yes |
| 7. Is there a description of how the study size was arrived at? | No |
| 8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for. | Yes |
| 9. Is information provided on participant eligibility? Consider if following provided: number potentially eligible, confirmed eligible, entered into study | No |
| 10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text. | Yes |
| 11. Is any sponsorship/conflict of interest reported? | Yes |
| 12. Finally…Did the authors identify any limitations and, if so, are they captured above? | Yes |
| | |

## 6. Use of baricitinib in patients with moderate to severe coronavirus disease 2019

| Criteria | Yes | No | Other (CD,NR,NA)* |
|---|---|---|---|
| 1. Was the study question or objective clearly stated? | Yes | | |
| 2. Were eligibility/selection criteria for the study population prespecified and clearly described? | Yes | | |
| 3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest? | Yes | | |
| 4. Were all eligible participants that met the prespecified entry criteria enrolled? | Yes | | |
| 5. Was the sample size sufficiently large to provide confidence in the findings? | | No | |
| 6. Was the test/service/intervention clearly described and delivered consistently across the study population? | Yes | | |
| 7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants? | Yes | | |
| 8. Were the people assessing the outcomes blinded to the participants' exposures/interventions? | | | NR |
| 9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis? | | | NA (retrospective study) |
| 10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes? | Yes | | |
| 11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)? | | | NA |
| 12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level? | | | NA |

**7. Baricitinib against severe COVID-19: effectiveness and safety in hospitalized pretreated patients**

| Criteria | Yes | No | Other (CD,NR,NA)* |
|---|---|---|---|
| 1. Was the study question or objective clearly stated? | Yes | | |
| 2. Were eligibility/selection criteria for the study population prespecified and clearly described? | Yes | | |
| 3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest? | Yes | | |
| 4. Were all eligible participants that met the prespecified entry criteria enrolled? | Yes | | |
| 5. Was the sample size sufficiently large to provide confidence in the findings? | | No | |
| 6. Was the test/service/intervention clearly described and delivered consistently across the study population? | Yes | | |
| 7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants? | Yes | | |
| 8. Were the people assessing the outcomes blinded to the participants' exposures/interventions? | | | NR |
| 9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis? | | | NA (retrospective study) |
| 10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes? | Yes | | |

| | | | |
|---|---|---|---|
| 11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)? | | | NA |
| 12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level? | | | NA |

**8. Baricitinib restrains the immune dysregulation in patients with severe COVID-19**

| | Yes | No | Unclear | Not applicable |
|---|---|---|---|---|
| 1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)? | ✔ | | | |
| 2. Were the participants included in any comparisons similar? | | ✔ | | |
| 3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest? | | ✔ | | |
| 4. Was there a control group? | ✔ | | | |
| 5. Were there multiple measurements of the outcome both pre and post the intervention/exposure? | | | ✔ | |
| 6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? | ✔ | | | |
| 7. Were the outcomes of participants included in any comparisons measured in the same way? | ✔ | | | |
| 8. Were outcomes measured in a reliable way? | ✔ | | | |
| 9. Was appropriate statistical analysis used? | ✔ | | | |

## LAMPIRAN 3

## HASIL PERHITUNGAN PERSETUJUAN

| | Pengamat 1 / reviewer 1 | | | |
|---|---|---|---|---|
| | | Ya | Tidak | Jumlah |
| Pengamat 2/ Rreviewer 2 | Ya | a | b | a + b |
| | Tidak | c | d | c + d |
| | Jumlah | a + c | b + d | a + b + c + d = n |

Ket :

Persetujuan = (a + d)/n

Cohens's Kappa = (Po-Pe)/(1-Pe)

Po= (a + d)/n

Pe = [(a + c) (a + b)/n + (b + d) (c + d)/n]/n

Kategori nilaai Cohen's Kappa

$0.00 \leq k \leq 0.20$ = Rendah

$0.21 \leq k \leq 0.40$ = Lumayan

$0.41 \leq k \leq 0.60$ = Cukup

$0.61 \leq k \leq 0.80$ = Baik

$0,81 \leq k \leq 1.00$ = Sangat Baik

**Skrining Fase 1 (TIAB *screening*)**

| | Reviewer 1 | | | |
|---|---|---|---|---|
| | | Included | Excluded | Jumlah |
| Reviewer 2 | Included | 19 | 0 | 19 |
| | Exluded | 0 | 859 | 859 |
| | Jumlah | 19 | 859 | 878 |

*Cohen's Kappa*= (Po-Pe)/(1-Pe) (1-0,95)/(1-0,95)= 0,05/0,05= 1

Po= (a + d)/n

Pe= [(a + c) (a + b)/n + (b + d) (c + d)/n]/n

Po = (19 + 859)/ 878 = 1

Pe = [((19 * 19)/878) + (859 * 859)/878))]878

= (361/878) + (737.881/878)/878

= (0,4 + 840,4)/878

Nilai Pesetujuan = Po* 100%

=1*100% 100%

**Skrining Fase 2 (*Full Text screening)***

| | | Reviewer 1 | | |
|---|---|---|---|---|
| | | Included | Excluded | Jumlah |
| Reviewer 2 | Included | 8 | 0 | 8 |
| | Exluded | 0 | 11 | 11 |
| | Jumlah | 8 | 11 | 19 |

*Cohen's Kappa*= (Po-Pe)/(1-Pe) (1-0,5)/(1-0,5)= 0,5/0,5= 1

Po= (a + d)/n

Pe= [(a + c) (a + b)/n + (b + d) (c + d)/n]/n

Po = (8 + 11)/ 19 = 1

Pe = [((8 * 8)/19) + (11 * 11)/19))]19

= (64/19) + (121/19)/19

= (3,3 + 6,3)/19

= 0,5

Nilai Pesetujuan = Po* 100%

=1*100%

= 100%