

# Variation in definition and measurement of primary outcomes in Cochrane systematic reviews of pharmacological treatment of stable COPD

Maekawa R<sup>1</sup>, Castillo M<sup>1</sup>, Huayanay L<sup>1</sup>

<sup>1</sup> Universidad Peruana Cayetano Heredia, Unidad de Epidemiología clínica, Perú

## Background:

An important element in defining the efficacy of a treatment is the appropriate selection of the primary outcome(s). Previous studies have demonstrated the heterogeneity of selection of primary outcome(s) in Cochrane systematic reviews (SR) that occurs between systematic reviews and between clinical trials of the same systematic review. The Task Force of American Thoracic Society and European Respiratory Society (ATS/ERS), published in 2008, Outcome for Pharmacological trial (1), that is considered as the basis for the core outcome set (COS) of pharmacological treatment of chronic obstructive pulmonary disease (COPD) according to COSMET (Core Outcome Measures in Effectiveness Trials) initiative(2). There is no previous study that compared the application of these recommendations in the Cochrane systematic reviews.

## Objectives:

1. To evaluate the concordance of definitions and measurements of the most frequent main results among systematic reviews on pharmacological treatment of stable COPD.
2. Evaluate if the most relevant outcomes follow the recommendations of the ATS/ERS task force

## Methods

Cochrane SR on stable COPD pharmacological treatment was selected between 2008 and 2019. Two investigators extracted the most frequent major outcomes from the Cochrane SR methods section. For each primary outcome, the definition and measurement method was extracted according to the systematic review. The concordance of these variables was evaluated among systematic reviews. It was checked if they meet the guidelines of the ATS/ ERS task force

## Results

We identified 25 systematic reviews on pharmacological treatment of stable COPD. The most frequent principal outcome were: exacerbation of COPD 21/25, quality of life 15/25, pulmonary function tests 8/25 and mortality 8/25. We consider the most relevant outcome the exacerbation of COPD . 18 RS were found where exacerbation was considered as the main outcome, whose differences in definitions, domain, specific metric(3,4) are shown in the table 1.

Most reviews do not show COPD exacerbation measurement method: written, electronic, patient or researcher source or medical history. It was observed that the results presented different measurement time (see table 2), only a few considered exacerbations more than 1 year, that is considered the ideal time (5).

The different definitions for COPD exacerbation were reviewed in the Nannini SR (Table 3)

The recommendations of the ATS/ERS task force proposed the definition of exacerbation of COPD would be an increase in respiratory symptoms over baseline that usually requires change in therapy(1).

**TABLE 1: Definitions, Domain, Specific metric in outcomes of COPD exacerbation in SR**

| SR | AUTHOR (#RCT)  | DEFINITION            | SPECIFIC METRIC  | DOMAIN                                       |
|----|--|-----------------------|--|--|
| 10 | Chong 2012(6); Welsh 2013(1), Karner 2014(14), Ni 2014(10), Rojas Reyes 2016(3) Horita 2017(9), Ni 2017(4), Ni 2018(2), Sliwka 2018 (2), Spencer (4) | AB, OC OR BOTH        | Patient with >=1 exacerbation  | Exacerbation Moderate or Severe exacerbation |
| 3  | Nannini 2012(9), Nannini2013(7),   | AB, OC OR HOSP        | Exacerbation rates per participant per year; patient with >=1 exacerbation; Hospitalisation due to exacerbation. | Exacerbation/Severe exacerb                  |
| 1  | Kew 2013(7)  | AB, OC OR HOSP        | Severe exacerbation  | Severe exacerbation                          |
| 1  | Tan 2016(0)  | AB, OC OR HOSP        | Acute exacerbation COPD  | Acute exacerbation COPD                      |
| 1  | Maqsood 2019(3)  | AB, CS, EMG OR HOSP   | Acute exacerbations of COPD  | Exacerbation                                 |
| 2  | Nannini 2013(7), Farne 2015(4)   | Different definitions | Hospital admission (exacerbation)  | Exacerbation                                 |
| 1  | OBA 2018 (21) Network metanalysis  | Not define            |  | Moderate or Severe exacerbation              |

**TABLE 3: Different definition of COPD exacerbation in Nannini 2013 SR**

| Trial                      | COPD exacerbation definition   |
|----------------------------|--|
| Calverley 2003             | Mild exacerbations = number of days with intake of 4 or more puffs of rescue medication<br>Severe exacerbation = intake of a course of oral steroids and/or antibiotics and/or hospitalisation due to respiratory symptoms   |
| Doherty 2012/Tashk in 2012 | Mild exacerbation = clinically judged deterioration of COPD symptoms (managed with increased short-acting bronchodilator use: ≥ 12 inhalations/d of SABA/short-acting anticholinergic, or ≥ 2 nebulised treatments/d of 2.5 mg SABA/short-acting anticholinergic) on any two consecutive days<br>Moderate exacerbation = clinically judged deterioration of COPD with an acute change in symptoms that required antibiotic and/or oral steroid treatment for lower airway disease<br>Severe exacerbation = deterioration of COPD that resulted in emergency treatment or hospitalisation due to COPD |
| Sin 2008                   | "Exacerbations were defined as worsening of COPD symptoms leading to hospitalisation, a visit to the emergency room, or use of an antimicrobial agent and/or systemic corticosteroids as an outpatient"  |
| Szafranski 2003            | Mild exacerbations = a day with ≥ 4 inhalations of reliever medication above the mean run-in use<br>Severe exacerbation = use of oral steroids and/or antibiotics and/or hospitalisation due to respiratory symptoms   |
| Tashkin 2008               | "Worsening of COPD symptoms that required treatment with oral corticosteroids and/or hospitalisation"  |
| TORCH                      | "A symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalisation, or a combination of these"   |
| TRISTAN                    | "Exacerbations were defined a priori as a worsening of COPD symptoms that required treatment with antibiotics, oral corticosteroids, or both. Episodes that required corticosteroid treatment or hospital admission were noted separately"   |
| Zhong 2012                 | "An exacerbation was defined as use of oral/IV corticosteroids and/or antibiotics and/or emergency room treatment/hospitalisation due to respiratory symptoms"   |

**TABLE 2: Length of studies in SR with outcomes of COPD exacerbation**

| TOTAL RS | AUTHORS   | LENGTH OF STUDY |
|----------|---|-----------------|
| 3        | NI 2018(2), SLIWKA 2018 (2), MAQSOOD 2019(3)  | <52W            |
| 10       | CHONG2012(6), KEW 2013(7), NANNINI 2013(7), NANNINI 2013(7), KARNER 2014(22), NI 2014(10), FARNE 2015(5), HORITA 2017(9), NI 2017(4), OBA 2018 (21/13), | > Y <52W        |
| 5        | SPRNCER 2011(4), NANNINI 2012(9), WELSH2013(1), ROJAS -REYES 2016(3), TAN (0)   | ≥52 W           |

## Conclusion

The primary outcome most frequently measured in the SRs was exacerbation of COPD, the definitions were similar among the systematic reviews but the concordance of the definitions among the trials of a systematic review was heterogeneous.

There were also discrepancies between the recommendations of the ATS / ERS working group for the definition and measurement of COPD exacerbation.

The editorial group could suggest that the authors describe more clearly the criteria for selecting the outcomes of the trials that were grouped in SR

## References

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Presenting autor and contact person:

Rosalba Maekawa

Rosalba.maekawa.y@upch.pe