Outcome Measures in Randomized Controlled Trials of Inhaled Asthma Medications: How often they are being put in practice

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ABSTRACT

Background - Asthma is a chronic inflammatory disorder of the airways. There is still no clear definition of asthma control and the criteria used in its evaluation varies from study to study. To address this problem, in 2006, the American Thoracic Society (ATS) proposed a list of outcome measures that clinical trials, aiming to study the effect of a therapeutic intervention on asthma control, should include and report both on baseline and during the study.

Aims – Main aims: To conclude if trials are using or not the minimum set of outcome measures recommended by the ATS. To analyse which measures are used the most and understand the evolution of measures taken through time. Secondary aim: To verify the influence between pharmaceutical industry sponsorship and outcome measures taken in each study.

Methods – Execute a systematic review. Searching for asthma randomized controlled trials (RCTs) on clinicaltrials.gov (American database) and clinicaltrialsregister.eu (European database) and reading them to verify if they fulfil all the eligibility criteria. All RCTs included in our participants group were analysed again in order to record which outcome measures were taken and if the study was or not sponsored by pharmaceutical industry. Finally, all data was organized and analysed using SPSS software.

Results – Of 142 RCTs found, only 17 fulfilled the eligibility criteria. On average, the trials used 3 recommended outcome measures. Before 2007, the studies were all registered on clinicaltrials.gov and had a mean of 5 measures used. After 2007, clinicaltrialsregister.eu was the dominant database and the mean was of 2 measures. An expressive number of trials used none of the recommended outcome measures (4 studies) and the majority used only a few. The most used measure was “pre BD FEV1” test and congregation of “composite scores”. The least used was “quality of life questionnaire” (the variable “others” was despised). There were no results concerning pharmaceutical sponsorship due to lack of information.
**Conclusions** – There is no evidence that the number of recommended outcome measures taken by RCTs has increased after 2007. It seems that the ATS guideline is not being followed, above all in the European trials.

**Key-words** – Asthma; asthma therapy; outcome measures; systematic review

**INTRODUCTION**

Asthma is a chronic inflammatory disorder of the airways, with an estimated 300 million individuals affected worldwide [1]. It is one of the most common chronic diseases. The prevalence of asthma has been increasing since 1960, especially in children [2]. Chronically inflamed airways are hyper-responsive to allergens, causing an inflammatory reaction and obstruction of the airways, which provokes wheezing, breathlessness, chest tightness and coughing, and may have negative consequences in the daily life of many patients [1, 3].

Asthma cannot be cured but it can efficiently be treated. Inhaled medication is the most frequently used because it brings drugs directly to the airways, resulting in a strong therapeutic effect, with fewer side-effects [1].

There are essentially two drug groups: controllers and relievers [1]. Controller drugs are used to avoid inflammatory reactions by inhibiting hyper-responsiveness and consequent obstruction of the airways [1]. Inhaled corticosteroids (ICSs) are a group of controller drugs that have proven to reduce asthma-related exacerbations that would lead to hospitalization and even death [4]. Reliever drugs are used to alleviate the effects of an asthma exacerbation, such as cough or chest tightness, usually by dilatation of smooth muscle of the airways. Short-acting Beta-2 agonists, also known as Beta-2 stimulants, are used as reliever drugs [1, 5, 6]. There is also long-acting beta-2 agonists used daily combined with ICSs to improve lungs function [5, 6].

Many studies, such as randomized controlled trials (RCTs), aim to evaluate the efficiency of many drugs in asthma therapy. Nevertheless, there is still no clear definition of asthma control and the criteria used in its evaluation varies from study to study. Because of this wide variety, comparison between studies and compilation of results, e.g. in meta-analysis, may become difficult [7].
To solve this problem, in 2006, the American Thoracic Society (ATS) proposed a list of outcome measures that clinical trials, aiming to study the effect of a therapeutic intervention on asthma control, should include and report both on baseline and during the trial [7].

Some of the outcome measures are very similar both on baseline characteristics and during the study: quantifying the symptom free days, analysing the reliever use, compositing scores (multiple tests - asthma control questionnaire/ asthma control test - applied have their scores combined to produce a composite score [7, 8]) and evaluating the quality of the patient’s life, usually measured by a questionnaire [7, 9]. On baseline characteristics ATS considers that the pre and pos bronchodilator forced expiratory volume in one second (pre BD FEV1 and pos BD FEV1) are important tests too [7, 10]. ATS also considers important the quantification of exacerbations within last 1-4 weeks on the assessment of treatment effect on current clinical control.

RESEARCH QUESTION AND AIMS

The main research question that we tried to answer was “Are randomized controlled trials that assess inhaled asthma therapy drugs using the minimum outcome measures recommended by the American Thoracic Society both on baseline and during the trial?”. As secondary research question we had “Is there any relation between pharmaceutical industry sponsorship and outcome measures taken?”

Our major aim was to analyse RCTs that assess inhaled asthma medication in order to determine if these trials were using the minimum set of outcome measures that were recommended by the ATS. We analysed which measures are used the most and tried to understand the evolution of measures taken both through time and before and after the ATS’s guideline.

We also aimed to understand the influence of the pharmaceutical industry sponsorship on the recommended outcome measures chosen by each RCT.
METHODS AND PARTICIPANTS

Study Participants

In order to identify the participants of our study, we consulted the clinicaltrials.gov and clinicaltrialsregister.eu databases with “asthma” as search term.

We selected only interventional studies phase III, closed, with results and whose participants were 12 years old or older.

We included a total of 142 RCTs, 61 on clinicaltrials.gov and 81 on clinicaltrialsregister.eu.

Study design

This study is a Systematic Review and we used randomized controlled trials as unit of analysis. We proposed to gather the information of different RCTs about outcome measures used in asthma therapy.

Data collection methods

Some of the points focused in the eligibility criteria were already mentioned on the advanced search of the databases, although it wasn't ensured that the specificity of the search was enough for the demand of our objectives.

For that reason, we created the following eligibility criteria for the selection of RCTs:

- About asthma;
- Randomized controlled trial phase III;
- English language;
- After 1980 (included);
- 12 years and older participants;
- Medication: beta-2-agonists and inhaled corticosteroids.
These criteria allowed us to screen the RCTs on basis of title and abstract. All the points had to be fulfilled. If one of them wasn’t, the RCT was automatically excluded.

![Method’s flowchart](image)

In a total of 142 RCTs selected from the advanced search, only 17 were included, 5 from clinicaltrials.gov and 12 from clinicaltrialsregister.eu. The other 125 were excluded, mainly because they did not broach uniquely asthma. After that, we read the trial’s registration characteristics, focusing on the methods part, in order to gather all information and proceed to statistical analysis.

**Statistical analysis**

The statistical analysis was carried out based on our final group of RCTs recruited. We organized all data using “SPSS” software and analysed if RCTs were following ATS’s guidelines. Other point of our focus was to verify if the RCTs in question were or not sponsored by pharmaceutical industry.

The variables we examined were year of publication, measures taken and sponsoring of pharmaceutical industry.
RESULTS

We began by analysing the frequency of each recommended outcome measure (in a total of 11) in all RCTs we have included. As we already focused, these measures were divided in two groups according to the time in which data was collected: baseline characteristics and assessment of asthma on current clinical control (during the trial).

In this first analysis, we only found one trial that mentioned the participants’ quality of life questionnaire both on baseline characteristics and during the study. The quantifying of relievers use was mentioned by 3 RCTs on baseline characteristics and by 4 during the study. Other 3 RCTs included the quantifying of exacerbations within last 1-4 weeks. The noting of symptom free days was done in 4 RCTs in both outcome measures’ groups. In what concerns to the composites scores, were mentioned by 4 RCTs on baseline characteristics and by 6 during the study. At last, the pre BD FEV1 test was mentioned by 10 RCTs and the pos BD FEV1 test by 7 (see figure 2).

The most used recommended outcome measure at baseline characteristics was pre BD FEV1 test and during the trial was the congregation of composite scores. The least used on both timings was quality of life questionnaire. It was also estimated the mean number of recommended outcome measures used in trials focused on asthma therapy. The result was about 3 measures each.

![Figure 2 - Recommended Outcome Measures’ Frequency in RCTs included; n=11](image)
After the first analysis, we compared the number of recommended outcome measures used by trial according to time and database it was searched.

So, we divided all the trials we included according to the database they were researched in. In clinicaltrials.gov (American database), the mean number of outcome measures used was 5.40 (5) and in clinicaltrialsregister.eu (European database) it was only 1.67 (2).

Before 2007, the mean number of outcome measures used was 5.25 (5) and after 2007 it was only 2.00 (2), which is very similar to the previous analysis because only 4 of the 17 studies were registered before the publication of ATS’s guideline and all of them on the American database. This constituted an important factor on the statistical analysis, in order not to be a confounding variable.

To verify if the results we obtained were statistically significant, we performed a t-test to compare the recommended outcome measures in the two databases we researched in and also between the RCTs that were published before and after 2007. As the number of participants of our study is low (the normality of the distribution is compromised) we had some doubts choosing if we should perform instead a non-parametrical test. We performed it too and the results found were very similar to the ones reported below.

In the first t-test (comparison between the two databases) we obtained a p-value of 0.002 and in the second t-test (comparison between the RCTs published before and after 2007) the p-value was 0.018, which means that both results were statistically significant. So, there is evidence that the number of recommended outcome measures used in the different studies has not increased both after 2007 and throughout time and has even decreased.

![Figure 3](image-url) – Number of Recommended Outcome Measures used by each RCT according to time and database it was searched. (Points in blue-clinicaltrial.gov database; points in white-clinicaltrialsregister.eu database); n=17
It’s important to emphasize that there were a meaningful number of trials that used none of the outcome measures (4 trials) and the majority used only a few.

There were no results concerning pharmaceutical sponsorship due to lack of information (only two of the studies weren’t sponsored).

DISCUSSION AND CONCLUSION

We had some limitations that have jeopardized the outcome of our work. One of them was the fact that all studies included in our systematic review that were registered before 2007 were all American and the ones post 2007 were almost all European. As the mean of measures taken has lowered after 2007, we can say that Europeans were not as rigorous (as Americans were even before the ATS’s guideline) concerning the number of outcome measures used.

With the results obtained with our systematic review, it seems that the ATS’s guideline is not being followed, as we have not found evidence that after 2007 the number of recommended outcome measures used in different studies increased.

We can conclude that RCT’s that assess inhaled asthma therapy drugs are using less than half of the minimum outcome measures recommended by the ATS’s guideline.
REFERENCES:


