ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
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«Αξιολόγηση της ποιότητας των αναφορών των τυχαιοποιημένων ελεγχόμενων κλινικών μελετών για τη χρήση των εισπνευστήρων ξηράς σκόνης (DPI's) σε ασθενείς με άσθμα που έχουν ανακοινωθεί από το 2010 έως το 2020 χρησιμοποιώντας την δήλωση CONSORT»

«Assess the reporting quality of Randomized-Controlled Trials for Dry Powder Inhalers in Asthma published from 2010 to 2020 using the CONSORT statement»

ΜΕΤΑΠΤΥΧΙΑΚΗ ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Της φοιτήτριας
Σαμπάνη Ανθής
ΑΕΜ: 0249

Τριμελής εξεταστική επιτροπή:
Στεφανίδης Ιωάννης (επιβλέπων)
Δοξάνη Χρυσούλα
Ζιντζαράς Ηλίας

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A. ABSTRACT

Background: Randomized Controlled Trials (RCTs) are a useful tool to evaluate the effectiveness of clinical interventions. The use of CONSORT (Consolidated Standards of Reporting Trials) statement is an evidence based approach to improve the quality of RCTs.
Objective: Evaluating the reporting quality of published RCTs for Dry Powder Inhalers in Asthma from 2010 to 2020 using the CONSORT statement-checklist.
Methods: We searched PubMed database for English-language RCTs involving patients with Asthma, who used asthma inhalers. Quality of reporting was assessed using a 37–item questionnaire based on the CONSORT checklist. Reporting was evaluated overall and according to journals' Impact Factor (IF).
Results: The search provided 59 eligible articles for evaluation. 16 of the 37-items were reported in a percentage of 43,24%, 25 out of 37- items were reported by 50% or more of the studies (67.57%), 12 out of the 37-items were reported in less than 50% of the total articles (32,43%), 5 out of the 37-items were reported in less than 10% of the studies (13,51%). Comparatively, about the 70% of the articles published both in higher or lower IF journals, reported a percentage of 55% or more of the 37-Items of the CONSORT statement.
Conclusions: The reporting quality of abstracts of RCTs on clinical pathway still should be improved. After the publication of CONSORT for abstracts guideline, the RCT abstracts reporting quality showed improvement to some extent.

Keywords: dry powder inhalers (DPIs), asthma, Randomized Controlled Trials, CONSORT statement

Α. ΠΕΡΙΛΗΨΗ

Εισαγωγή: Οι ΤΚΔ αποτελούν σημαντικό εργαλείο για την εκτίμηση της αποτελεσματικότητας των κλινικών παρεμβάσεων. Η χρήση της δήλωσης CONSORT ειναι μια προσέγγιση βάσει αποδεικτικών στοιχείων, προκειμένου να βελτιωθεί η ποιότητα των ΤΚΔ.
Στόχοι: Στην παρούσα μελέτη, αξιολογήθηκε η ποιότητα αναφοράς των δημοσιευμένων ΤΚΔ για τη χρήση των εισπνευστήρων ξηράς σκόνης (DPI's) σε ασθενείς με άσθμα που έχουν ανακοινωθεί από το 2010 εως το 2020 χρησιμοποιώντας την δήλωση CONSORT.
Μέθοδοι: Πραγματοποιήθηκε αναζήτηση των κατάλληλων ΤΚΔ σε αγγλική γλώσσα, που αφορούσαν σε ασθενείς με άσθμα που χρησιμοποιούσαν εισπνεόμενη αγωγή. Η αναφερόμενη ποιότητα εκτιμήθηκε σύμφωνα με το 37- στοιχείων ερωτηματολόγιο της δήλωσης CONSORT. Επιπλέον, τα άρθρα κατηγοριοποιήθηκαν και εκτιμήθηκαν σε σχέση με το Impact Factor των περιοδικών που τα δημοσίευσαν.
Αποτελέσματα: Στη μελέτη συμπεριελήφθησαν 59 ΤΚΔ που πληρούσαν τα κριτήρια επιλογής για έλεγχο. Τα 16 από τα 37-στοιχεία αναφέρονται σε ποσοστό 43,24%, τα 25 από τα 37-στοιχεία αναφέρονται σε ποσοστό 50% ή περισσότερο (67.57%), τα 12 από τα 37-στοιχεία αναφέρονται σε μικρότερο ποσοστό του 50% (32,43%), ενώ τα 5 από τα 37-στοιχεία αναφέρονται σε ποσοστό μικρότερο του 10% των συνολικών άρθρων (13,51%). Συγκρτικά, περίπου το 70% των άρθρων που δημοσιεύτηκαν σε περιοδικά με χαμηλότερο ή υψηλότερο IF (σε σχέση με το Διάμεσο) ανέφεραν σε ποσοστό 55% ή περισσότερο τα στοιχεία της δήλωσης CONSORT.
Συμπεράσματα: Συμμόρφωση στη δήλωση CONSORT 2010 συνεπάγεται βελτίωση της ποιότητας των αναφορών των ΤΚΔ.

Keywords: εισπνευστήρες ξηράς σκόνης (DPIs), άσθμα, τυχαιοποιημένες κλινικές δοκιμές (ΤΚΔ), δήλωση CONSORT

Συντομογραφίες /Abbreviations:

- ΤΚΔ: Τυχαιοποιημένη Κλινική Δοκιμές
- RCT: Randomized Controlled Trial
- Dry Powder Inhalers (DPIs)
- CONSORT: **CON**solidated **S**tandards **O**f **R**eporting **T**rials

B. INTRODUCTION

Randomized Controlled Trials (RCTs), when properly designed, conducted and reported are a gold standard in clinical medicine and public health, in order to evaluate the efficacy of new clinical interventions, as they minimize bias and provide the basis for valid statistical analysis.

However, in various fields of medicine, RCTs suffer from important methological limitations. In response to this concern, of misleading evaluation and its consequences, an international group of scientists and journals editors developed the CONSORT statement to improve the quality of reporting of RCTs. It was first published in 1996, last revised in 2010 and translated in 13 languages. The 2010 CONSORT statement comprises a checklist of 25 items (37 items/sub-items) that should be included in reports of RCTs and a diagram for documenting the flow of participants through a trial. The CONSORT is not meant to be a quality judgment tool and should not be used to this direction, but rather as evidence based guide for proper reporting of RCTs.

The main objective of this study is to assess the reporting quality of RCTs that explore the efficacy and safety of Dry Powder Inhalers in asthmatic patients, based on CONSORT checklist 2010. There is a number of articles that have assessed the reporting quality o RCTs in asthma, however, no study has evaluates the reporting quality of RCTs focusing on the use of DPIs in asthmatic patients.

Asthma is a serious global health problem affecting all ages of groups. Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with a variable expiratory airflow limitation (GINA 2020). The goals of asthma management are to achieve good symptom control and to minimize the risk of asthma- related mortality. The main treatment of asthma includes the administration of medication with inhalers. There are different types of inhalers which suit different people such as pressurized metered dose inhalers (MDIs), breath –activated inhalers (DPIs), inhalers with spacer devices and nebulizers. Poor inhalation is a significant problem in asthma because the individual does not receive an adequate dose of the prescribed drug that leads to reduced therapy and control of asthma. Uncontrolled asthma has a major effect on the quality of life of the patients.

C. METHODS

Selection of studies

PubMed was searched to identify RCTs that investigate the efficacy and safety of Dry Powder Inhalers in Asthma the last decade, from 2010 till 2020. The search criterion was the following term: “DPIs in Asthma”. Search was limited to the following criteria: “Randomized Controlled Trial”, English language and inclusion of studies on “human” subjects.

Reporting assessment tool

The assessment of reporting were evaluated according to the revised CONSORT 2010 checklist which includes a 37-item questionnaire (http://www.consort-statement.org).

Eligibility criteria

Studies that fulfilled the following criteria were considered eligible: (1) they were classified as RCTs -RCTs (2) they were published from 2010 till 2020 (3) all the studies performed on humans (4) reports published in English language.

Studies were excluded according to the following criteria: • reports not published in English • conference abstracts • studies performed on animals • other study designs (e.g. retrospective study design, prospective not randomized design) • study protocols • retracted papers. We screened all titles and abstracts retrieved, as well as full texts in case of inability to establish if a study met the inclusion criteria.

All Journals were searched and listed according to the Impact Factor for 2019.

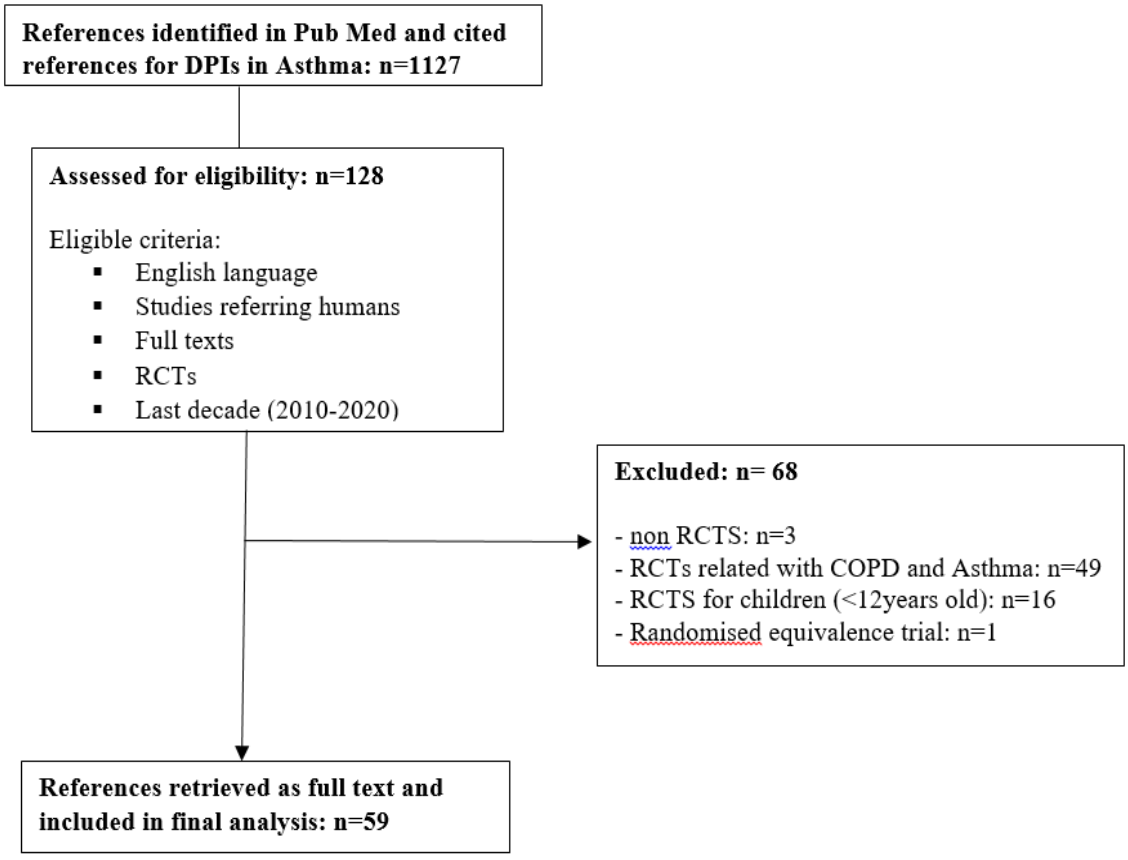


Figure 1: Flow diagram of citations through the retrieval and screening process

Objectives

The primary endpoint of the present study was to assess the reporting quality of RCTs that explore the efficacy and safety of Dry Powder Inhalers in asthmatic patients, based on CONSORT checklist 2010.

Methological evaluation-Statistical analysis

All the articles included were read in-depth. During the evaluation procedure we followed the following steps:

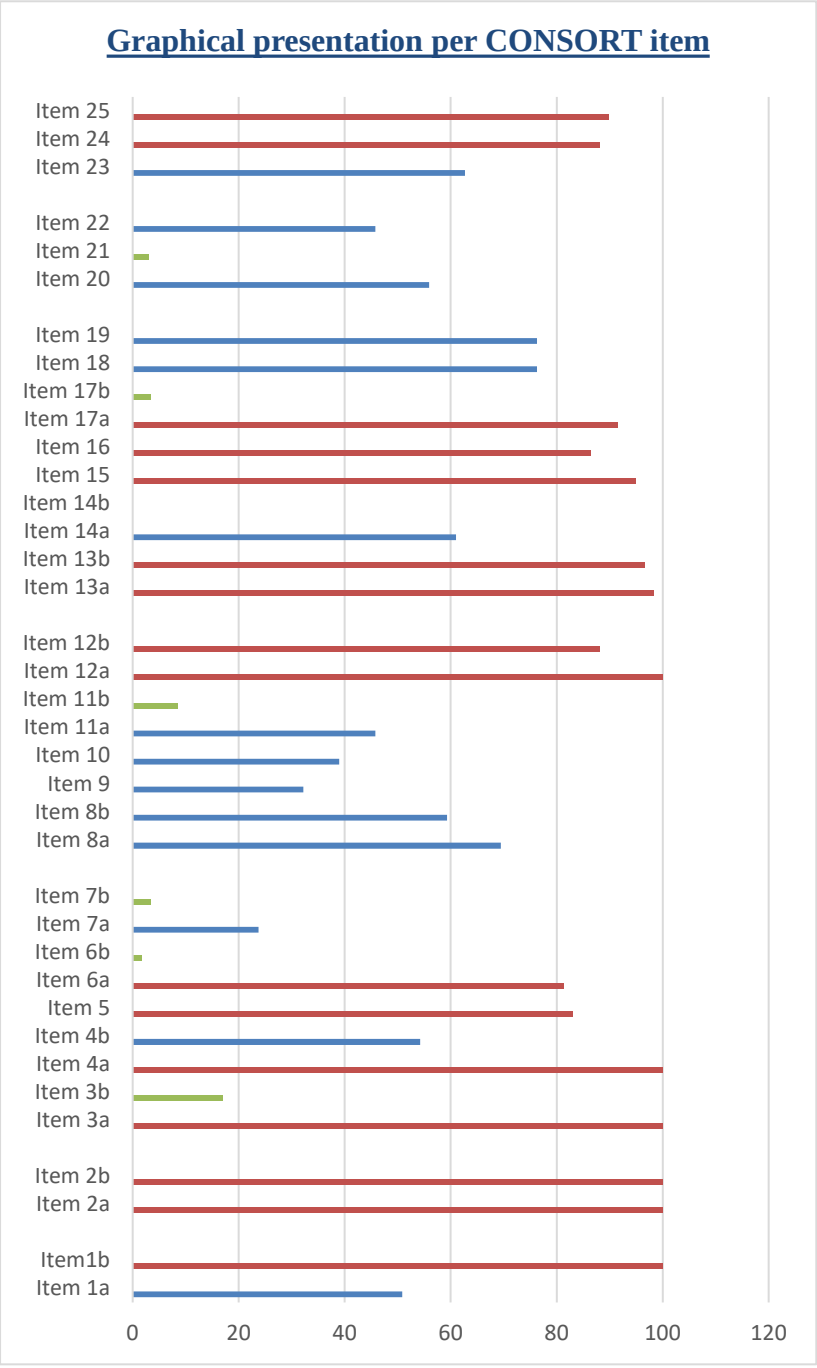
- All items were investigated in terms of whether they were reported. Each item can be characterized as “yes” if it was clearly and adequately reported, and “no” if it was partially reported, or not reported at all.
- When an item was reported in a different section of the trial it was considered as positive response.
- Revised CONSORT version of 2010 was used for all extracted articles.
- There was a comparison among articles that were published in higher and lower rank journals according to the Median Impact Factor of the year 2019 for the specific articles.

Comparison among the items reported and the Median Impact Factor was made by using the Pearson chi-square test. We divided articles into two groups to compare the adherence to the CONSORT statement of the articles in higher rank and lower rank to median Impact Factor of the year 2019 for the included articles. The cut off point for statistical significance was set the 0.05 level.

D. RESULTS

Table 1 shows the overall frequency of reporting of the 37items of the CONSORT statement. The overall reporting of CONSORT checklist items ranges from 1.69% to 100%. In detail, 16 items out of the 37 (43.24%) items/sub-items were reported by 80% or more of the studies (items 1b, 2a 2b, 3a, 4a, 5, 6a, 12a, 12b, 13a, 13b, 15, 16, 24, 25). 6 out of 37 items (16.21%) were reported in all studies (items 1b, 2a, 2b, 3a, 4a, 12a). Furthermore, 25 out of 37 (67.57%) items were reported by 50% or more of the studies (including the 16 items mentioned above).

Some of the items were reported only by a small proportion of articles. 12 out of the 37 items were reported in less than 50% of the total articles (items 3b, 6b, 7a, 7b, 9, 10, 11a, 11b, 14b, 17b, 21, 22). Five of these items were mentioned in less than 10% of the studies (6b, 7b, 11b, 14b, 17b).



- 16 of the 37-items were reported in a percentage of 43,24%.
- 25 out of 37- items were reported by 50% or more of the studies (67.57%)
- 12 out of the 37-items were reported in less than 50% of the total articles (32,43%)
- 5 out of the 37-items were reported in less than 10% of the studies (13,51%)

CONSORT Section/topic	Item No	All trials No= 59
Title and abstract		
	1a	30 (50.85%)
	1b	59 (100%)
Introduction		
Background and objectives	2a	59 (100%)
	2b	59 (100%)
Methods		
Trial design	3a	59 (100%)
	3b	10 (16.95%)
Participants	4a	59 (100%)
	4b	32 (54.24%)
Interventions	5	49 (83.05%)
Outcomes	6a	48 (81.35%)
	6b	1 (1.69%)
Sample size	7a	14 (23.73%)
	7b	3 (5.08%)
Randomization		
Sequence generation	8a	41 (69.49%)
	8b	35 (59.32%)
Allocation concealment mechanism	9	19 (32.20%)
Implementation	10	23 (38.98%)
Blinding	11a	27 (45.76%)
	11b	6 (10.17%)
Statistical methods	12a	59 (100%)
	12b	52 (88.14%)
Results		
Participant flow (a diagram is strongly recommended)	13a	58 (98.30%)
	13b	57 (96.61%)
Recruitment	14a	36 (61.02%)
	14b	N/A
Baseline data	15	56 (94.91%)
Numbers analysed	16	51 (86.44%)
Outcomes and estimation	17a	54 (91.52%)
	17b	2 (3.39%)
Ancillary analyses	18	45 (76.27%)
Harms	19	45 (76.27%)
Discussion		
Limitations	20	33 (55.93%)
Generalisability	21	18 (30.50%)
Interpretation	22	27 (45.76%)
Other information		
Registration	23	37 (62.71%)
Protocol	24	52 (88.13%)
Funding	25	53 (89.83%)

Table 1: Reporting of CONSORT Items

Table 2 shows the reporting of CONSORT items and differences in compliance among articles published in Journals according the Median Impact Factor for 2019.

The 56.89% of the articles were published in journals with an Impact Factor lower to Median (IF< 2.846). From the articles published in Journals with an IF < Median, only 5 out of 25 reported the items of CONSORT statement in a percentage of 75% or more (20%). Respectively, only 2 out of 33 article that were published in journals with higher IF reported the CONSORT items in a percentage of 75% or more (6.06%). In addition, about the 70% of the articles published in higher or lower IF, reported a percentage of 55% or more of the 37-Items of the CONSORT statement.

Nevertheless, there is no statistically significance between the reported items among the articles published in higher and lower Impact Factor. The only item reported with a p-value <0.05 was item No 5, with a p-value 0.021, which was statistically significant.

Items No	IF>2.846 (MEDIAN) n=25	IF<2.846 (MEDIAN) n=33	P-VALUE
1a	15 (60%)	15 (45.45%)	0.272
1b	25 (100%)	33 (100%)	-
2a	25 (100%)	33 (100%)	-
2b	25 (100%)	33 (100%)	-
3a	25 (100%)	33 (100%)	-
3b	4 (16%)	6 (18.18%)	0.827
4a	25 (100%)	33 (100%)	-
4b	16 (64%)	16 (48.48%)	0.239
5	23 (92%)	22 (66.67%)	0.021
6a	20 (80%)	27 (81.82%)	0.861
6b	1 (4%)	N/A	-
7a	7 (28%)	7 (21.21%)	0.549
7b	2 (8%)	1 (3.03%)	0.397
8a	20 (80%)	21 (63.63%)	0.175
8b	14 (56%)	20 (60.60%)	0.742
9	10 (40%)	9 (27.27%)	0.306
10	12 (48%)	11 (33.33%)	0.258
11a	13 (52%)	14 (42.42%)	0.469
11b	6 (24%)	N/A	-
12a	25 (100%)	33 (100%)	-
12b	22 (88%)	29 (87.88%)	0.988
13a	25 (100%)	32 (96.97%)	-
13b	24 (96%)	32 (96.97%)	0.841
14a	16 (64%)	20 (60.60%)	0.791
14b	N/A	N/A	-
15	23 (92%)	32 (96.97%)	0.397
16	23 (92%)	27 (81.82%)	0.265
17a	22 (88%)	31 (93.94%)	0.424
17b	1 (4%)	1 (3.03%)	0.841
18	18 (72%)	27 (81.82%)	0.374
19	18 (72%)	26 (78.79%)	0.549
20	13 (52%)	20 (60.60%)	0.512
21	9 (36%)	9 (27.27%)	0.476
22	12 (48%)	15 (45.45%)	0.847
23	18 (72%)	19 (57.57%)	0.257
24	24 (96%)	27 (81.82%)	0.1
25	23 (92%)	29 (87.88%)	0.609

Table 2: Reporting of CONSORT items in compliance among articles published in journals according to MEDIAN impact factor 2019 (one article out of 59 is excluded due to not having an IF for 2019)

IF	(45-55) (%)	(55-65) (%)	(65-75) (%)	(75-85) (%)	Total (%)
IF> 2,846 MEDIAN)	7 (28)	6 (24)	7 (28)	5 (20)	25 (100)
IF< 2,846 (MEDIAN)	8 (24.24)	15 (45.45)	8 (24.24)	2 (6.06)	33 (100)
Total	15 (25.86)	21 (36.02)	15 (25.86)	7 (12.07)	58 (100)

Table 3: Reporting of CONSORT items among articles published in higher or lower Impact Factor

E. DISCUSSION

The present study explored the reporting quality of RCTs for DPIs in Asthma based on the CONSORT statement.

The study has some limitations: the research has been restricted in PubMed, which is the most common used database in medicine and did not extent to other databases. In addition, only articles published in English were considered, which may lead to language bias. However, this risk is limited since none of the articles, captured by our search strategy were published in other languages. Another limitation is the selection of a specific age group (adolescents and adults), although asthma is affecting all group of ages.

The study has, also, several strength, because in the study included articles published in medical journals that clinicians can find in the PubMed database, and the methodology of this study is easily reproducible.

In this study 16 of the 37-items were reported in a percentage of 43,24%, 25 out of 37-items were reported by 50% or more of the studies (67.57%), 12 out of the 37-items were reported in less than 50% of the total articles (32,43%), 5 out of the 37-items were reported in less than 10% of the studies (13,51%), as shown from the table 1, and the graphical presentation of CONSORT per item above.

A percentage of more than 27% of the RCTs that were assessed, are presenting the items of Title and abstract- 1b (100%)**,** Background and objectives- items 2a,2b (100%), Trial design- item 3a (100%), Participants- item 4a (100%), Interventions- item 5 (83.05%), Outcomes- item 6a (81.35%), Statistical methods-items 12a (100%), 12b (88.14%), Participant flow- item 13a (98.3%), Baseline data- item 15 (94.91%), Numbers analyzed-item 16 (86.44%), Outcomes and estimation- item 17a (91.52%), Protocol– item 24 (88.13%) and Funding- item 25 (89.83%).

It is important to mention that some of the items were not adequately reported, like the item 6b (reported only in one article, 1,69%), item 7b (reported in a percentage of 5,08%), item 17b (reported in 2 articles, 3,39%).

In terms of analysis the relation between the reported items of CONSORT statement from the articles evaluated and the journals Impact Factor, our study showed no statistical significance. Almost half of the RCTs that published in both high and low rank Impact Factor journals reported a percentage of 55% or more of the 37-Items of the CONSORT statement, while only 5 out of 25 (20%), and 2 out of 33 (6,06%) reported a percentage of 75% or more of the 37-Items of the CONSORT statement.

Our results suggest that the quality of reporting in the contemporary literature on DPIs in asthma remains suboptimal. We have identified deficiencies in reporting specific areas that need to be improved. All of the CONSORT items that we examined were adequately described in at least one article, which indicates that improved reporting is certainly possible. Improved awareness of the CONSORT statement by researchers, reviewers, and journal editors is likely to improve reporting quality, and by extension significant improvement of the patients therapeutic response.

F. CONCLUSION

In conclusion, this study shows that the reporting quality of Randomized-Controlled Trials for Dry Powder Inhalers in Asthma published from 2010 to 2020 using the CONSORT statement is suboptimal.

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