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Laboratory of Biomathematics

Director: Professor ZINTZARAS ELIAS

Master of Science thesis

«Εκτίμηση της ποιότητας αναφοράς των RCTsγια την φαρμακευτική θεραπεία της προκαλούμενης από χημειοθεραπεία περιφερικής νευροπάθειας (CIPN) που δημοσιεύτηκαν κατά την περίοδο 2005-2015 χρησιμοποιώντας την CONSORTαναφορά»

"Assessment of the reporting quality of RCTs for pharmaceutical treatment of Chemotherapy Induced Peripheral Neuropathy published from 2005-2015 using the CONSORT statement"

By

APOSTOLOS GIANNOUSAS

Master of Science program: Biomedical Research Methodology, Biostatistics and Clinical Bioinformatics

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Contents

1. Abstract

Introduction:Many drugs such as antidepressants, anticonvulsants and opioidshave been used in the management of Chemotherapy Induced Peripheral Neuropathy. However, the reporting quality of their Randomized Controlled Trials (RCTs) has not been yet assessed.

Objective: This study aims to assess the reporting quality of RCTS for pharmaco-therapeutic drugs usually used in the treatment of Chemotherapy Induced NeuropathicPain published from 2005-2015, using the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement.

Methods: PubMed and Cochrane CENTRAL databases were searched in August 2016 for relative RCT reports. Each item of the CONSORT 2010 checklist was scored with 1 if clearly reported or 0 otherwise. Total CONSORT scores and frequencies of reporting each item were calculated. Comparisons between pre- and post- CONSORT 2010 periods were made with Mann- Whitney and Fisher exact tests.

Results: The total CONSORT score of the 9 articles, in the combined 2005-2015 period, ranged from 20 to 28. Items of the CONSORT checklist were reported in different sequences. 6 items were recorded in 100% of the articles though 11 items were reported in less than 50%. Between pre- and post-CONSORT 2010 period groups, we can see important progress in reporting Additional analysis(Item12b, $p=0,003<0.05$) and Generalisability (Item2, $p=0,023<0.05$).

Conclusion: Some aspects of the study are inadequately reported. To raise the reporting quality of RCTs on pharmaceutical treatment of CIPN, further progress is needed.

2. Introduction

Chemotherapy-inducedperipheralneuropathy(CIPN)isacommontreatment-relatedadverseeffect of anticancer drugs including platinums, taxanes, epothilones, vinca alkaloids, and newer agents such as bortezomiboccurring in ~20% of patients given standard doses of chemotherapy, althoughthispercentagevariesdependingonchemotherapyregimens,durationofexposure,andassessmentmethods and in almost 100% of patients treated with high doses.It affectslong-termqualityoflife andhasthepotentialtoresultinchemotherapydosereductionsand/orearlydiscontinuation. CIPN presents clinically as deficits in sensory, motor, and sometimes autonomic function. Sensory disturbances range from a mild tingling sensation to spontaneous burning pain and hypersensitivity to stimuli. These symptoms often affect both hands and feet and may spread into a 'glove/stocking' distribution. Symptoms are usually symmetrical distally but may be more severe unilaterally. Although dependent on the specific agent, the feet are often affected first. Symptoms may occur at any time during the course of chemotherapy (seen with paclitaxel), or even after termination (commonly known as "coasting"), which refers to neuropathic symptoms that present after discontinuation of

anticancer treatment, and which may continue or worsen over weeks or months. This phenomenon suggests that there is ongoing neuronal damage even after discontinuation of anticancer drugs.

As far as the pathophysiology of CIPN is concerned, many mechanisms including mitochondrial dysfunction, various pain mediators and abnormal spontaneous discharge in A and C fibershave been suggested. It is a fact that CIPN is usually under-treated, partly because of the lack of a consensus on its pathophysiology.

And although some data suggest that certain substances may prevent CIPN, no treatments have been demonstrated to prevent and treat it effectively. Pregabalin may be used to decrease neuropathy after oxaliplatin treatment. Duloxetine showed modest analgesic efficacy in CIPN (paclitaxel- and oxaliplatin-induced) patients compared with a placebo in a randomized clinical trial. These data support a moderate recommendation for CIPN treatment. Among antidepressants, venlafaxine has been shown to reduce the incidence of CIPN, albeit with some side effects. Cannabinoids may be a new treatment option for CIPN, and should be evaluated in robust RCTs. Although tricyclic antidepressants (such as nortriptyline or desipramine), gabapentin, and a topical gel containing baclofen (10 mg), amitriptyline HCL (40 mg), and ketamine (20

mg) yielded inconclusive data in CIPN trials, these agents may constitute the remaining CIPN treatment options.

RCTS are considered as a gold standard in the evaluating process of new interventions through the comparison with standard treatment or placebo. In order to provide strong medical evidence, they must lie on strict methodology and should be clearly and adequately reported. Randomization, allocation, blinding are some key aspects of the value of a trial. Implementation weaknesses and/or poor reporting can mislead to biased results affecting health care providers and even health policy makers. Additionally, a complete and transparent RCT report can elucidate any methodological drawbacks of the study, revealing its credibility.

Aiming to improve the reporting quality of RCTs, the CONSORT (Consolidated Standards of Reporting Trials) statement was first developed in 1996. Since then it has been revised twice, in 2001 and in 2010. The last revision has provided a 25-item checklist that every trial should address in its report (see Appendix), and a flow diagram describing the subjects flow through the trial procedures. While the CONSORT statement can be applied in RCTs in general, it focuses on randomized trials with two parallel arms. For other study types and intervention types (herbal medicinal products, acupuncture, non- pharmacologic) several CONSORT extensions have been developed. There are

also CONSORT extensions for harms and abstracts. All these products are accessible through the website www.consort-statement.org.

Since its appearance, CONSORT statement gains increasing support from more than 400 medical journals. Even significant editorial groups like international Committee of Medical Journal Editors and the Council of Science Editors endorse it, leading to reporting quality improvement.

There is a number of published reviews assessing the reporting quality of RCTs in several medicinal subspecialty. Generally, they conclude that there is some improvement through the years but not at an expected level. In the field of Chemotherapy Induced Peripheral Neuropathy, progress is made in understanding the pathogenesis mechanisms and leads to the use of new drugs. As a result more and more RCTs are designed and conducted to evaluate these drugs. However the reporting quality of RCTsfor pain alleviating drugs in chemotherapy induced pain, so far, is not known. This knowledge would contribute to trial replication and to the credibility of results of RCTs. Health care providers and policy makers could draw safer conclusions evaluating the efficacies of the different agents and designing therapeutic strategies.

In this context, aim of this study is to assess the reporting quality of RCTs for pharmaceutical treatment of Chemotherapy

Induced pain published from 2005-2015.

3. Methods

3.1 Search strategy

PubMed and Cochrane central databases were searched in August 2016 for reports on RCTs involving pharmaceutical treatment in Chemotherapy Induced Peripheral Neuropathy. On PubMed the following search terms were used: “CIPN AND treatment”, “CIPN AND antidepressants”, “CIPN AND anticonvulsants”, “CIPN AND Opioids”. The filters “article type” , “Humans” and “publication date” were customized as “Randomized Controlled Trials” and “from 01/01/2005 to 31/12/2015” respectively. The same search terms were used on Cochrane CENTRAL database setting the following search limits: database as “Trials” and publication date as “between 2005 and2015”.

The initial search conducted for “CIPN AND treatment” demonstrated the antidepressants, the anticonvulsants and the opioids as the three main categories of drugs used in the treatment of CIPN. Thus, taking into consideration the literature as well, it was decided to broaden the search using these 3 terms.

What is more, because of the fact that year 2016 has not yet come to an end, data from 2005 to 2015 were used for the conduction of the search.

3.2 Eligibility criteria- study selection

Type of studies: eligible were only RCTs. To consider a study as RCT, participating subjects should have been randomized in at least two arms. Other types of studies such as retrospective, animal, genetic association studies were excluded.

Type of participants: no limitations regarding to age, gender, origin.

Type of intervention: eligible were studies testing antidepressants, anticonvulsants and opioids as drugs used in the treatment of CIPN. Acupuncture,Physiotherapy and other types of intervention were set as an exclusion criterion.

Type of disease: RCTs were eligible, if they clearly stated that the intervention was tested for CIPN (Chemotherapy Induced Peripheral Neuropathy). Other types of neuropathy, such as diabetic neuropathy, were also exclusion criteria

Type of publication: eligible were only full articles, written in English language, published in biomedical journals from 01/01/2005 to 31/12/2015. Abstracts, editorials, reviews, meta-analyses, letters and other type of publication were to be

excluded from the analysis.

From the records identified, duplications and abstracts were removed. Then an initial screening was performed on the basis of title and the remaining articles were read in abstract and full text to apply the eligibility criteria and select the reports included in the analysis. References of the articles included in the analysis were screened in order not to lose any relative reports unidentified with the initial search.

3.3 Data extraction and assessment of reporting quality according to CONSORT statement

The selected articles were assessed for reporting quality using the revised CONSORT 2010 checklist (www.consort-statement.org). This checklist is a questionnaire with25 items and totally 37 (sub-)items, evaluating if several aspects of the trial are reported and not whether they are implemented. Following the relevant guidelines, each (sub-)item for each eligible article was scored separately with 1 or 0. 1 was scored when the item was clearly reported in the article. Negative or alternative responses apart from yes and no were scored as 0. Thus, a total CONSORT score for each article was obtained with maximum probable total CONSORT score being equal to 37.

3.4 Data analysis

Total CONSORT scores of articles were analyzed initially using descriptive statistics methods. Taking into consideration that the revised CONSORT2010 checklist was first introduced in 2010, three period groups were formed: one including articles from 2005 to 2010, another including articles published from 2010 to 2015 and a combined group, taking all articles together. Medians and means were calculated. Pre- and post-

CONSORT groups were compared in total CONSORT scores to test for significant differences using Mann- Whitney U test for 2 independent samples.

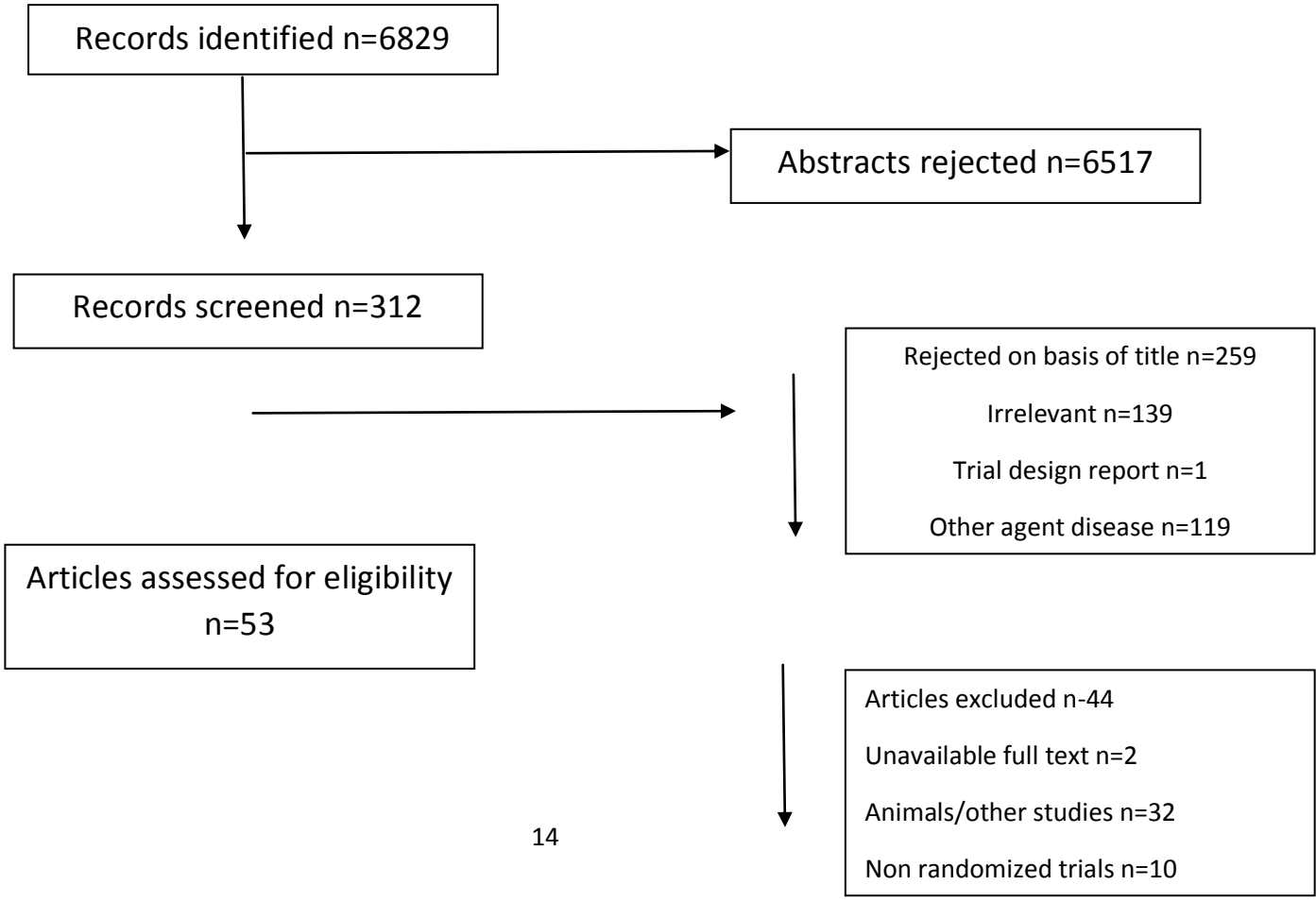
Frequencies for each reporting item of the checklist were calculated for pre-, post- CONSORT and combined period group of articles. Additionally, it was intended to examine whether the reporting quality of trials improved after the introduction of the 2010 revised version of CONSORT. To achieve that, a Fisher exact test between the two period groups (pre- and post-CONSORT) was to be performed. Due to the small size of pre- and post- CONSORT 2010 groups, the Pearson's chi-square test was rejected and results were interpreted cautiously.

Categorical data were processed, frequencies were calculated and statistical tests were performed using IBM SPSS v21 statistics package, provided by University of Thessaly. A P-value of 0.05 was set as a threshold of statistical significance.

4. Results

4.1 Search results

6829 records were identified searching PubMed. 6517 abstracts were removed as a consequence of search limits mentioned above. After that, screening on the remaining 312 records was performed and 259 were rejected on the basis of title. The 53 reports left were assessed for eligibility, regarding abstracts and full text articles. Finally, 9 articles were included in the analysis. (Figure 1)



Articles included in the analysis
n=9

Figure 1. Flow diagram of the study selection process

4.2 Study Characteristics

2 RCTs were published in Cancer Research Journal, 2 in Journal of Pain and Symptom Management, 2 in Supportive Care in Cancer, 1 in International Journal of Clinical Practice, 1 in Journal of The American Medical Association and 1 in Annals of Oncology. There were 6 publications in the pre-CONSORT 2010 period (2005-2010), and 3 publications after 2010. Three major categories of pharmaceutical agents as well as combinations of the drugs of these categories, as tested intervention, were met: Anti-convulsants (Pregabalin, Lamotrigine and Gabapentin) in 3 reports, anti-depressants (Venlafaxine,Amitriptyline,Duloxetine) in 3 reports andCannabinoidand ketamine in 1 reporteach, amitriptyline with ketamine in 1 report and finally baclofen, amitriptyline and ketamine in 1 also.

		Number of RCTs
Journal	• *International Journal of clinicalPractice* • *Journal of American medical association* • *Journal of pain and symptom management* • *Cancer research* • *Supportive care in cancer* • *Annals of oncology*	*1* *1* *2* *2* *2* *1*
Funding sources	• *Pharmaceutical industries* • *Other*	*7* *2*

Tested intervention	• *Anticonvulsants*
	  ○ *Lamotrigine*
	  ○ *Gabapentin*
	  ○ *Pregabalin*
	• *Antidepressants*
	  ○ *Venlafaxine*
	  ○ *Duloxetine*
	  ○ *Amitriptyline*
	• *Cannabinoids*
	• *Ketamine*
		3
		1
		1
		1
		5
		1
		1
		3
		1
		2

Control	• *Placebo* • *Other pharmaceutical substance*	*7* *2*
RCT arms	• *2* • *>2*	*9* *0*
Age of participants	• *Adults* • *Children*	*9* *0*
Type of study (center)	• *Single- center* • *Multi-center*	*2* *7*
Blinding	• *Blinded* • *Open- label*	*8* *1*
CONSORT 2010 flow	• *Disposable*	*9*

diagram	• *Not disposable*	*0*

RCT*: Randomized Controlled Trial*

CONSORT*: Consolidated Standards of Reporting Trials*

Table 1. Characteristics of RCTs included in the analysis

4.3 Reporting Quality

The total CONSORT score of RCT reports, including the period 2005-2015, ranged from 20 to 28 with a mean of 22 and a median equal to 21 (mean=22, SE=1,215 , SD=3,647 , median= 21). Regarding the pre- and post-CONSORT period, mean total CONSORT scores were 23and 20 respectively. No statistically significant difference in total CONSORT score between pre- and post-CONSORT 2010 period groups was found (P=0,243>0.05, Mann Whitney U test). In table 2, the scoring process of the articles according to CONSORT 2010 checklist and the total scoresare presented.

In table 3, items of the CONSORT 2010 checklist are reported in different frequencies among the articles included in the analysis. Abstract(Item 1b), Background(Item 2a), Eligibility criteria(Item 4a), Outcomes(Item 6a), Participant flow(Item 13a) and Baseline(Item 15) are reported in all of the 9 RCTs. None of the RCTs report interim analysis(Item 7b) which refers to explanation of any interim analysis and stopping guidelines. Binary outcomes(Item 17b) which indicatespresentation of both absolute and relative effect sizes is not also reported in any of the 9 articles.

7 items have a frequency of 89% in the period 2005-2015. These are: Title(Item1a), Objectives(Item2b), Statistical methods(Item12a), Losses and exclusions (Item13b), Outcomes and estimations(Item17a), Harms(Item19) and Interpretation(Item22). Funding(Item25), Generalisability(Item22) and Numbers Analyzed (Item16) are reported in 78% of RCTs. The following most reported items are Protocol(Item24), Registration(Item 23), Additional analysis(Item12b), Type of randomization(Item8b), Intervention(Item5) and Trial design(Item3a) with a 67% proportion. Allocation sequence(Item8a) and Recruitment(Item14a) are reported in about half of RCTs, with a proportion of 56%. Less than half of articles report Allocation concealment(Item9) and Settings(Item4b) with a proportion of 45%. 33% report Limitations(Item20) and Blinding(Item11a). 4 items are reported in 22% of articles, including Trial end(Item14b), Sample size(Item7a), Changes to outcomes(Item6b) and changes to methods(Item3b). Ancillary analysis(Item18) and Similarity of interventions(Item11b) have a reporting frequency equal to 11%. Frequency of the 37 reporting items for the pre- and post-CONSORT 2010 period are shown in Table 3.

Between pre- and post-CONSORT 2010 period groups, we cannot see important progress in reporting Additional analysis(Item12b, $p=0,003<0.05$) and Generalisability(Item21, $p=0,023<0.05$).

Table 2. Scores of selected RCT reports using CONSORT 2010 checklist

DATA ITEMS	RCT_1	RCT_2	RCT_3	RCT_4	RCT_5	RCT_6	RCT_7	RCT_8	RCT_9
1a. Title	1	1	1	1	0	1	1	1	1
1b.Abstract	1	1	1	1	1	1	1	1	1
2a.Background	1	1	1	1	1	1	1	1	1
2b.Objectives	1	1	1	1	1	1	1	0	1
3a.Trial design	1	0	1	1	0	1	1	0	1
3b.Changes to methods	0	0	0	1	0	0	0	0	1
4a.Eligibility criteria	1	1	1	1	1	1	1	1	1
4b.Settings	0	0	1	0	1	0	1	0	1
5.Interventions	0	1	1	0	1	1	1	1	0
6a.Outcomes	1	1	1	1	1	1	1	1	1
6b.Changes to outcomes	0	0	0	1	0	0	0	1	0
7a.Sample size	0	0	0	0	0	1	0	0	1
7b.Interim analysis	0	0	0	0	0	0	0	0	0
8a.Allocation sequense	1	1	1	0	0	0	0	1	1
8b.Type of randomization	1	1	0	0	0	1	1	1	1
9.Allocation concealment	0	1	0	0	0	0	1	1	1
10.Implementation	1	0	0	0	0	0	0	0	0
11a.Blinding	0	1	0	0	0	1	0	1	0
11b.Similarity of interventions	0	0	0	1	0	0	0	0	0
12a.Statistical methods	0	1	1	1	1	1	1	1	1
12b.Additional analysies	0	1	0	0	1	1	1	1	1
13a.Participant flow	1	1	1	1	1	1	1	1	1
13b.Losses and exclusions	1	1	1	1	0	1	1	1	1
14a.Recruitment	0	1	1	1	0	1	0	0	1
14b.Trial end	1	0	0	0	0	0	0	0	1
15.Baseline data	1	1	1	1	1	1	1	1	1
16.Numbers analysed	1	0	1	1	1	1	1	0	1
17a.Outcomes and estimations	1	1	0	1	1	1	1	1	1
17b.Binary outcomes	0	0	0	0	0	0	0	0	0
18.Ancillary analyses	0	0	0	0	0	1	0	0	0
19.Harms	1	1	0	1	1	1	1	1	1
20.Limitations	0	1	0	0	0	0	1	0	1
21.Genaralisability	0	1	0	1	1	1	1	1	1
22.Interpretation	1	1	1	0	1	1	1	1	1
23.Registration	1	1	1	0	0	1	1	0	1
24.Protocol	1	1	1	0	0	1	1	0	1
25.Funding	1	1	1	1	1	1	1	0	0
Total score	21	25	20	20	17	26	25	20	28

Table 3. Proportion of reporting of 37 data items in a total of 9 RCTs on treatment of CIPN by publication period from 2005-2015 (post-, per-CONSORT 2010 and combined)

DATA ITEMS	pre-CONSORT 2010(n=6)	post-CONSORT 2010 (n=3)	combined 2005-2010 (n=9)	p-value
1a. Title	83,3% (n=5)	100% (n=3)	89% (n=8)	0,453
1b.Abstract	100% (n=6)	100% (n=3)	100% (n=9)	
2a.Background	100% (n=6)	100% (n=3)	100% (n=9)	
2b.Objectives	83,3% (n=5)	100% (n=3)	89% (n=8)	0,453
3a.Trial design	50% (n=3)	100% (n=3)	67% (n=6)	0,134
3b.Changes to methods	17% (n=1)	33% (n=1)	22% (n=2)	0,571
4a.Eligibility criteria	100% (n=6)	100% (n=3)	100% (n=9)	
4b.Settings	50% (n=3)	33% (n=1)	45% (n=4)	0,635
5.Interventions	83,3% (n=5)	33% (n=1)	67% (n=6)	0,134
6a.Outcomes	100% (n=6)	100% (n=3)	100% (n=9)	
6b.Changes to outcomes	17% (n=1)	33% (n=1)	22% (n=2)	0,571
7a.Sample size	33,3% (n=2)	0	22% (n=2)	0,257
7b.Interim analysis	0	0	0	
8a.Allocation sequense	50% (n=3)	67% (n=2)	56% (n=5)	0,635
8b.Type of randomization	83,3% (n=5)	33% (n=1)	67% (n=6)	0,134
9.Allocation concealment	67% (n=4)	0	45% (n=4)	0,058
10.Implementation	0	33% (n=1)	11% (n=1)	0,134
11a.Blinding	50% (n=3)	0	33% (n=3)	0,134
11b.Similarity of interventions	0	33% (n=1)	11% (n=1)	0,134
12a.Statistical methods	100% (n=6)	67% (n=2)	89% (n=8)	0,134
12b.Additional analysies	100% (n=6)	0	67% (n=6)	**0,003**
13a.Participant flow	100% (n=6)	100% (n=3)	100% (n=9)	
13b.Losses and exclusions	83,3% (n=5)	100% (n=3)	89% (n=8)	0,453
14a.Recruitment	50% (n=3)	67% (n=2)	56% (n=5)	0,635
14b.Trial end	17% (n=1)	33% (n=1)	22% (n=2)	0,571
15.Baseline data	100% (n=6)	100% (n=3)	100% (n=9)	
16.Numbers analysed	67% (n=4)	100% (n=3)	78% (n=7)	0,257
17a.Outcomes and estimations	100% (n=6)	67% (n=2)	89% (n=8)	0,134
17b.Binary outcomes	0	0	0	
18.Ancillary analyses	17% (n=1)	0	11% (n=1)	0,453
19.Harms	100% (n=6)	67% (n=2)	89% (n=8)	0,134
20.Limitations	50% (n=3)	0	33% (n=3)	0,134
21.Genaralisability	100% (n=6)	33% (n=1)	78% (n=7)	**0,023**
22.Interpretation	100% (n=6)	67% (n=2)	89% (n=8)	0,134
23.Registration	67% (n=4)	67% (n=2)	67% (n=6)	1
24.Protocol	67% (n=4)	67% (n=2)	67% (n=6)	1
25.Funding	67% (n=4)	100% (n=3)	78% (n=7)	0,257

P-values obtained from Fisher exact tests.

5. Conclusion

Nowadays, more and more pharmaco-therapeutic drugs arise in the field of CIPN treatment. The current study aimed to assess the quality of RCTs on pharmaceutical treatment of chemotherapy induced peripheral neuropathy using the revised CONSORT 2010 statement and examine the CONSORT 2010 effect on improving the reporting quality over time.

However, the overall reporting quality of the selected RCTs stands on an average level without significant differences between pre- and post-CONSORT 2010 publication periods. Furthermore, reporting items are documented in a wide range of frequenciesacross the sum of the articles. Among the most frequently recorded items the following ones are included: Baseline data(Item15:the table showing baseline demographic and clinical characteristics for each group), Background(Item2a:Scientific background and explanation of rationale), Abstract(Item1b:Structured summary of trial design, methods, results, and conclusions), Participant flow(Item12a:For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome), and Eligibility criteria(Item4a:Eligibility criteria for participants). Conversely, identification as an RCT in the title, blinding, trial end, limitations, sample size and type of randomization seems really problematic. CONSORT 2010 adversely effects significantly on reporting Additional analysis and Generalisability.

Some of the items can be considered as key methodological items, because they can help reader to assess the validity of RCT. Blinding, allocation concealment and randomization implementation are significant to avoid bias.

In this study, assessing the reporting quality of RCTs on pharmaceutical treatment of Chemotherapy Induced Peripheral Neuropathy during the last 10 years, conclusions about CONSORT 2010 effect on improving the reporting quality are not considered as credible. We have to mention that this might have become as a result of the small size of pre- and post-CONSORT 2010 publication period groups (3 on the post- and 6 on the pre-CONSORT 2010 group) and especially the small size of the pre-CONSORT 2010 group.

Furthermore, this study has more limitations. Firstly, the assessment of RCT reports was conducted by only one person, the author. Probably the review by a second person would diminish the subjective factor. Secondly, the search was restrained in only 2 databases: PubMed and Cochrane Library and took under investigation only those published in English language and only for Humans. In contrast to those limitations, strength of this study is that all items of the last revised 2010 CONSORT checklist were used in the process.

Finally, RCTs on pharmacological treatment of Chemotherapy Induced Peripheral Neuropathy published from 2005-2015 have insignificant reporting quality assessed using the CONSORT statement. Despite the fact that several items are well reported, poor reporting of some critical items makes the reports susceptible to bias, reduces their assessment to generate medical evidence and consequently limits health care decision. As new methods of treatment of CIPN are evolving, substantial obedience of their RCT reports to CONSORT statement is obliged in order to assess effectively their validity. Broader recommendations of CONSORT statement by medical journals would also contributeto plainly improved reporting quality.

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7. Appendix

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specificobjectivesorhypotheses	
Methods			
Trialdesign	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Samplesize	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
	8a	Method used to generate the random allocation sequence	

Sequencegeneration	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocationconcealmentmechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statisticalmethods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation,together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baselinedata	15	A table showing baseline demographic and clinical characteristics for each group	
Numbersanalysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	

	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillaryanalyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.