**ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ**
**ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ**
ΠΜΣ «Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική και Κλινική Βιοπληροφορική»

Master of Science Thesis:

**Assessment of the reporting quality of RCTs for Memantine treatment in Dementia published from 2000 to 2019 using the CONSORT statement.**

Μεταπτυχιακή Διπλωματική Εργασία (ΜΔΕ) με τίτλο:

Αξιολόγηση της ποιότητας καταγραφής των Τυχαιοποιημένων Κλινικών Δοκιμών (ΤΚΔ) για τη θεραπεία Μεμαντίνης στην Άνοια, που εκδόθηκαν από το 2000 έως το 2019, χρησιμοποιώντας τη δήλωση CONSORT.

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Λάρισα, Σεπτέμβριος 2019

**Αφιερώνεται στην οικογένειά μου.**

# Contents

# 1. ABSTRACT

**Introduction:** Memantine is a main therapeutic agent in the treatment of Dementia. Randomized Controlled Trials (RCTs) are fundamental in medical research. Reporting quality of RCTs is based on CONSORT (CONsolidated Standards Of Reporting Trials) Statement.

**Objectives:** This study aims to assess the reporting quality of RCTs for Memantine treatment in Dementia published from 2000 to 2019, based on a checklist originating from the CONSORT statement.

**Methods:** Pubmed and Cochrane Databases were searched for published RCTs. Eligible RCTs were as follows: Published in English, from 2000 to 2019, including Dementia patients randomly assigned to at least two medicinal arms, one of these was Memantine treatment arm. Reporting quality was assessed using a 38-item checklist based on CONSORT statement. The primary outcome was the calculation of the mean Overall Compliance metric, using descriptive statistics.

**Results:** Thirty eligible trials were analyzed. The average Overall CONSORT compliance was 47.5% (41.5% - 53.4%). The percentage of RCTs with more than 75% overall compliance was 0%.

**Conclusion:** The study shows that the reporting quality of RCTs for Memantine treatment in Dementia, published between 2000 and 2019, is generally poor.

**Keywords:** CONSORT, RCTs, Randomized controlled trials, Dementia, Alzheimer's disease, Memantine.

**ΠΕΡΙΛΗΨΗ**

**Εισαγωγή:** Η Μεμαντίνη είναι μία σημαντική θεραπευτική ουσία για την αντιμετώπιση της Άνοιας. Οι Τυχαιοποιημένες Κλινικές Δοκιμές (ΤΚΔ) είναι το θεμέλιο της ιατρικής έρευνας. Η ποιότητα καταγραφής των ΤΚΔ βασίζεται στη δήλωση CONSORT (Consolidated Standards of Reporting Trials, Ενισχυμένα Πρότυπα Αναφοράς Δοκιμών).

**Στόχοι:** Η μελέτη αυτή, βασιζόμενη σε μία λίστα ελέγχου που προέρχεται από τη δήλωση CONSORT, στοχεύει να αξιολογήσει την ποιότητα καταγραφής των ΤΚΔ της Μεμαντίνης ως θεραπείας της Άνοιας, που εκδόθηκαν από το 2000 έως το 2019.

**Μέθοδοι:** Έγινε αναζήτηση των εκδοθεισών ΤΚΔ στις Βάσεις Δεδομένων Pubmed και Cochrane. Οι επιλέξιμες ΤΚΔ ήταν ως εξής: Εκδοθείσες στα Αγγλικά, από το 2000 έως το 2019, που περιελάμβαναν ασθενείς με Άνοια, τυχαία κατανεμημένους σε δύο τουλάχιστον ομάδες φαρμακευτικής θεραπείας, εκ των οποίων μία είχε τη Μεμαντίνη. Η ποιότητα καταγραφής αξιολογήθηκε εφαρμόζοντας μία λίστα ελέγχου 38 αντικειμένων, με βάση τη δήλωση CONSORT. Το πρωταρχικό αποτέλεσμα ήταν ο υπολογισμός της μέσης βαθμολογίας συνολικής συμμόρφωσης, χρησιμοποιώντας περιγραφική στατιστική.

**Αποτελέσματα:** Τριάντα μελέτες που πληρούσαν τις προϋποθέσεις αναλύθηκαν. Η μέση συνολική συμμόρφωση CONSORT ήταν 47.5% (41.5% - 53.4%). Το ποσοστό των ΤΚΔ με συμμόρφωση ανώτερη του 75% ήταν 0%.

**Συμπέρασμα:** Αυτή η μελέτη δείχνει ότι η ποιότητα καταγραφής των ΤΚΔ της Μεμαντίνης ως θεραπείας της Άνοιας, που εκδόθηκαν από το 2000 έως το 2019, είναι γενικά φτωχή.

**Λέξεις – κλειδιά:** Ενισχυμένα Πρότυπα Αναφοράς Δοκιμών, ΤΚΔ, Τυχαιοποιημένες Κλινικές Δοκιμές, Άνοια, Νόσος Αλτσχάιμερ, Μεμαντίνη.

## 2. INTRODUCTION

Dementia could be simply defined as the syndrome of substantial global cognitive decline not attributable to alteration in level of consciousness[1]. More precisely, according to ICD-11: "Dementia is an acquired brain syndrome characterized by a decline from a previous level of cognitive functioning with impairment in two or more cognitive domains (such as memory, executive functions, attention, language, social cognition and judgment, psychomotor speed, visuoperceptual or visuospatial abilities). The cognitive impairment is not entirely attributable to normal aging and significantly interferes with independence in the person's performance of activities of daily living. Based on available evidence, the cognitive impairment is attributed or assumed to be attributable to a neurological or medical condition that affects the brain, trauma, nutritional deficiency, chronic use of specific substances or medications, or exposure to heavy metals or other toxins"[2]. It can be described as a syndrome usually of a chronic or progressive nature. We can find many different forms of dementia. Alzheimer disease is the most common form (60–70%) of cases. Other major forms include vascular dementia, dementia with Lewy bodies, and a group of diseases that contribute to frontotemporal dementia. The boundaries between different forms of dementia are not completely clear. Worldwide, around 50 million people have dementia, with nearly 60% living in low- and middle-income countries. Every year, we expect nearly 10 million new cases[3].

Memantine (IUPAC Name: 3,5-dimethyladamantan-1-amine) is a voltage-dependent, moderate-affinity uncompetitive NMDA-receptor antagonist. It modulates the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction. EMA has approved this drug for the treatment of adult patients with moderate to severe Alzheimer's disease[4]. It is used either as a monotherapy or in combination with cholinesterase inhibitors. Memantine is a safe and effective drug that merits further research on several topics[5]. A recent meta-analysis study comparing safety and effectiveness of cholinesterase inhibitors and Memantine found that Memantine had the best profile of acceptability[6].In general, Memantine has a strong sales potential in the market, due to Dementia epidemics combined with the global aging of population.

Randomized Controlled Trials (RCTs) are commonly believed to be the gold standard for Medicine, providing the highest grade of evidence. RCTs' value derives from the implementation of strict methodology along with clear reporting[7,8]. Peer reviews and unbiased systematic reviews are based on the quality of RCTs reporting. Biased results from poorly designed and reported trials can mislead decision making in health care at all levels[9]. Unfortunately, trial reports often omit methodological details[10]. An overwhelming body of evidence stating that the completeness of reporting of RCTs is not optimal has accrued over time[11]. Against this deficiency, a multinational team of medical journal editors, clinical trialists, epidemiologists, and methodologists, developed the CONSORT (CONsolidated Standards Of Reporting Trials) Statement. This is an evidence-based, minimum set of recommendations for reporting randomized trials that offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation. Its first edition came in 1996 and its most recent revision is the CONSORT 2010 Statement, which consists of a 25-item checklist and a participant flow diagram, along with some brief descriptive text[12]. Despite the fact that adoption of CONSORT reporting guidelines has helped to improve the quality of research reports, guidelines remain much less adhered to than they should be[13].

The objective of this study is to assess the reporting quality of RCTs for Memantine treatment in Dementia, in articles published from 2000 to 2019. As evaluation tool we used the CONSORT 2010 statement.

# 3. METHODS

## 3.1. Data Sources and Search Strategy

PubMed and Cochrane databases were searched for RCTs on Memantine treatment in Dementia published from January 1, 2000 to September 2, 2019. On Pubmed we used as a search criterion the MeSH terms "memantine" and ("dementia" or "alzheimer"). Additionally, we used the "randomized controlled trial" as Publication Type, "2000/01/01": "3000" as Publication Date, "English" as language and "Humans" for species as filters. On Cochrane we also used as a search criterion the phrases "memantine" and ("dementia" or "alzheimer") and "randomised clinical trial" in Title or Abstract or Keyword terms, limited to "article" as Publication Type, with Publication Year from 2000 to 2019, in Trials.

## 3.2. Eligibility criteria

Trials were eligible for inclusion if the participants had been randomly assigned to at least two medicinal treatment arms and included patients with all different types of Dementia disease. At least one arm should have been Memantine treatment (either as monotherapy or combined therapy). Articles were included only if they were published in English, from 2000 to 2019.

Reports of trials on non-medicinal regimens, no Memantine treatment, dose comparison or pharmacokinetic studies, small pilot studies, extension studies or sub-studies, alongside any article with information resulting from a previously conducted trial (post-hoc or secondary or sub-group analysis) were excluded. Crossover studies were also excluded due to their specific design.

## 3.3. Reporting Assessment tool

To assess the reporting quality of the eligible RCTs, we used the CONSORT 2010 checklist (http://www.consort-statement.org/) –see also APPENDIX A- which consists of 25 items with sub-items (in total 37 items). We have included as an additional item (No 13) whether the article contains or not a participant flow diagram (in order to implement the CONSORT authors' strong recommendation of using one). Thus, our final list consists of 38 items.

CONSORT 2010 checklist applies to every section of an RCT article, in reference to all critical points of a clinical trial. Use of this checklist was made strictly according to the guidelines of the CONSORT explanation and elaboration document (available at the above mentioned CONSORT website). Additionally for the items 1b (Structured summary) and 19 (Harms), we used the CONSORT recommended specific extensions for Abstracts and Harms respectively (also available at the above mentioned CONSORT website).

We must note that the CONSORT statement was revised in 2010. Out of the total 30 eligible studies, 12 were published before 2010, whereas 18 were published from 2010 to 2019. We used the same revised version for all of them.

## 3.4. Evaluation - Analysis

The author reviewed all selected articles one by one and investigated each item of the CONSORT checklist in terms of whether they were reported or not, assigning a positive response (1= YES) or a negative response (0 = NO) respectively. The search was only for reporting the items, not for actual performance of these items during the clinical trial. We must note that we assigned a positive response only if the item's report followed the CONSORT instructions to the letter, meaning that the report of the item should cover every detailed point of it, according to the CONSORT explanation and elaboration document.

When an item was reported in at least one of the following 5 sections of the article (Title / Abstract, Introduction, Methods, Results, Discussion) but not on the specific one that CONSORT demands, e.g. item 3a "Trial Design" reported in Title or Introduction but not on Methods, the response was negative. On the contrary, the items 23 - 25 regarding Other Information were checked as positive response regardless where it was reported.

When an item was not applicable in a clinical trial or when it was not obvious whether the criterion of reporting was met, the item was considered as non –reported (negative response).

The reported items were categorized into 5 groups as follows: (1) Title / Abstract and Introduction, (2) Methods, (3) Results, (4) Discussion, (5) Other Information.

The RCTs were also classified based on different characteristics, as follows:

- Publication period – 2 groups – (1) 2000 – 2009 (before CONSORT revision), (2) 2010 – 2019 (after CONSORT revision)
- Current Journal Impact Factor (IF 2018) – 3 groups – (1) low (IF < 3), (2) medium (3 ≤ IF < 7), (3) high (IF ≥ 7). The IF was accessed through the Clarivate Analytics Journal Citation Reports website[14].
- CONSORT current endorsement – 2 groups – (1) non – endorsement, (2) endorsement. The status of CONSORT current endorsement for each journal was accessed through the CONSORT website[15].
- Trial size, according to the number (n) of participants randomized – 3 groups – (1) small (n < 30), (2) medium (30 ≤ n < 100), and (3) large (n ≥ 100).

The primary outcome was the calculated **"Overall CONSORT compliance"**, which is the percentage of the 38 items that each article reported. Descriptive analysis of this score was based on Means, 95% Confidence Interval and Medians. Additionally, we identified the article which had the maximum score.

As a co-primary outcome, we also calculated the **"Greater than 75% overall compliance"**, meaning the percentage of the articles reporting at least 75% of the 38 checklist items. The above mentioned metric was considered to be an appropriate cutoff in other similar studies[16]. It is important to note that some of the items were not applicable in most of the trials. These were item No 3b (changes to methods), 6b (changes to trial outcomes), 7b (interim analyses), 14b (trial termination) and 17b (effect size of binary outcomes). If we cut the above mentioned items out, the maximum score of CONSORT compliance would be only 86.8%.

Additionally, as secondary outcomes, we made comparison of the median "Overall CONSORT compliance" between the different categories based on appropriate non-parametric tests (Mann –Whitney U for the comparison between the 2 Publication periods, Kruskal – Wallis for the comparison between the 3 groups of Impact Factor, Mann –Whitney U for the comparison between the 2 groups of CONSORT endorsement, Kruskal – Wallis for the comparison between the 3 groups of Trial size).

Moreover, we calculated for each publication period the **"Item CONSORT compliance"**, meaning the percentage of articles reporting a specific item. We also calculated the **"CONSORT compliance per group of items"**, meaning the percentage of the grouped items that each article reported, and the **"Greater than 75% compliance per group of items"**, meaning the percentage of the articles reporting at least 75% of the grouped items, for each one of the 5 groups of items (Title / Abstract and Introduction, Methods, Results, Discussion, Other Information).

It is important to note that the whole evaluation procedure (Database search, Review of articles and Statistics) was performed by only one person, the author of this study.

All statistical analyses were performed with use of IBM SPSS v.25.0 package and Microsoft Excel 2010 software. All statistical tests were carried out at the 95% level of significance.

# 4. RESULTS

## 4.1. Search results

The evaluation procedure was performed in five steps, as we can see in the search flow chart (Figure 1). Pubmed search and Cochrane search, according to the eligibility criteria, returned 102 and 11 RCTs articles, respectively. After rejection of 7 duplicate articles (which were included in both databases), we reviewed 106 articles by title. Forty five articles were excluded due to irrelevance, not referring to randomized trials, or referring to Post – hoc analysis. In the next step, 61 remaining articles were reviewed by abstract and 16 of them were excluded either for the same above mentioned reasons, or due to referring to secondary analysis, or due to republication. One more article was excluded due to inaccessibility. The remaining 44 articles were reviewed by full text, 14 of which were excluded either for all the above mentioned reasons, or due to referring to extension study, or sub-study. Finally, 30 articles were included in the study, which were thoroughly reviewed in terms of compliance to the CONSORT 2010 checklist.

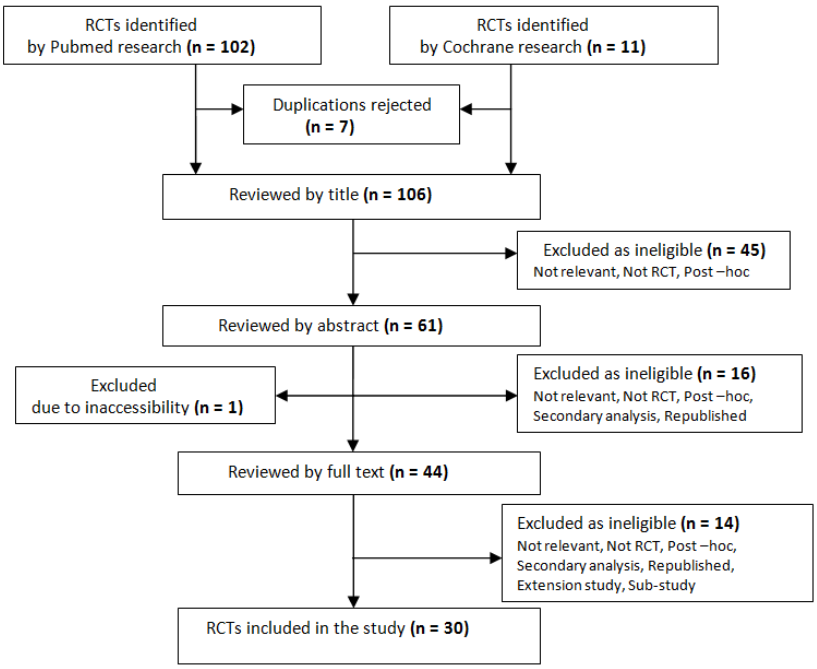


**Figure 1.** *Systematic Review flow chart*

A list of these 30 RCTs can be found in the APPENDIX – B. Categorization of these articles can be found in Table 1. Twelve articles were published between 2000 and 2009, whereas 18 articles were published between 2010 and 2019. The articles were hosted in a total of 21 different journals. Seven articles were published in journals with low Impact Factor (IF < 3), 14 articles were published in journals with medium Impact Factor (3 ≤ IF < 7), 9 articles were published in journals with high Impact Factor (IF ≥ 7). Moreover, 19 articles were published in journals that do not endorse the CONSORT statement, whereas 11 articles were published in journals that endorse the CONSORT statement. At last, the selected 30 RCTs included a total of 7,321 randomized patients. Three of the trials referred to a small sample size (n <30), 6 trials referred to a medium sample size (30 ≤ n < 100) and 21 trials referred to a large sample size (n ≥ 100).

| | | Frequency of RCTs | % |
|---|---|---|---|
| **Journal** | AIDS | 1 | 3,33 |
| | Alzheimer Dis Assoc | 1 | 3,33 |
| | Am J Geriatr Psychia | 1 | 3,33 |
| | CNS Drugs | 1 | 3,33 |
| | Curr Alzheimer Res | 1 | 3,33 |
| | Curr Med Res Opin | 1 | 3,33 |
| | Eur J Neurol | 1 | 3,33 |
| | Int Clin Psychopharm | 1 | 3,33 |
| | Int J Geriatr Psychiatry | 1 | 3,33 |
| | Int Psychogeriatr | 1 | 3,33 |
| | J Alzheimers Dis | 6 | 20,00 |
| | J Am Med Dir Assoc | 1 | 3,33 |
| | J Clin Psychopharmacol | 1 | 3,33 |
| | J Neurol Neurosurg Psychiatry | 1 | 3,33 |
| | JAMA | 2 | 6,67 |
| | Lancet | 1 | 3,33 |
| | Lancet Neurol | 3 | 10,00 |
| | N Engl J Med | 2 | 6,67 |
| | Neurosci Behav Physiol | 1 | 3,33 |
| | PLoS One | 1 | 3,33 |
| | Stroke | 1 | 3,33 |
| **Publication Period** | 2000-2009 | 12 | 40 |
| | 2010-2019 | 18 | 60 |
| **Impact Factor** | low(IF<3) | 7 | 23,33 |
| | medium (IF 3-7) | 14 | 46,67 |
| | high (IF>7) | 9 | 30,00 |
| **CONSORT endorsement** | NO | 19 | 63,33 |
| | YES | 11 | 36,67 |
| **Trial size** | small (n<30) | 3 | 10 |
| | medium (n = 30 -100) | 6 | 20 |
| | large (n >100) | 21 | 70 |

**Table 1.** *Characteristics of RCTs included in the analysis*

## 4.2. Reporting quality results

The "Overall CONSORT compliance", alongside with the "CONSORT compliance per group of items" for each one of the 5 groups of items, calculated for each one of the 30 articles separately, can be seen in the Table 2. The Mean "Overall CONSORT compliance" was 47.5% (41.5% - 53.4%) and the Median "Overall CONSORT compliance" was 51.5%. The article with the maximum score (74%) was RCT id 10 (1st Author: *Hanney*, Journal: *Lancet*, Year: *2012*).

The "CONSORT compliance per group of items" was as follows: 59.2% (Title /Abstract and Introduction), 44.2% (Methods), 47.9% (Results), 61.2% (Discussion), 35.5% (Other Information). Aggregated results per time period can be also seen in Figure 2.

| | | | | CONSORT compliance | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RCT id | First Author | Journal | Year | Overall | | Title/Abstract and Intro | | Methods | | Results | | Discussion | | Other information | |
| | | | | (n =38) | percentage | (n =4) | percentage | (n =17) | percentage | (n =11) | percentage | (n =3) | percentage | (n =3) | percentage |
| 30 | Orgogozo | Stroke | 2002 | 11 | **0,29** | 3 | 0,75 | 2 | 0,12 | 4 | 0,36 | 2 | 0,67 | 0 | 0 |
| 29 | Wilcock | Int Clin Psychopharm | 2002 | 17 | **0,45** | 2 | 0,5 | 9 | 0,53 | 5 | 0,45 | 1 | 0,33 | 0 | 0 |
| 28 | Reisberg | N Engl J Med | 2003 | 14 | **0,37** | 1 | 0,25 | 6 | 0,35 | 4 | 0,36 | 2 | 0,67 | 1 | 0,33 |
| 27 | Tariot | JAMA | 2004 | 20 | **0,53** | 3 | 0,75 | 9 | 0,53 | 5 | 0,45 | 2 | 0,67 | 1 | 0,33 |
| 26 | Peskind | Am J Geriatr Psychia | 2006 | 19 | **0,5** | 3 | 0,75 | 8 | 0,47 | 6 | 0,55 | 1 | 0,33 | 1 | 0,33 |
| 25 | van Dyck | Alzheimer Dis Assoc | 2007 | 14 | **0,37** | 2 | 0,5 | 5 | 0,29 | 5 | 0,45 | 1 | 0,33 | 1 | 0,33 |
| 24 | Schifitto | AIDS | 2007 | 14 | **0,37** | 1 | 0,25 | 6 | 0,35 | 6 | 0,55 | 1 | 0,33 | 0 | 0 |
| 23 | Bakchine | J Alzheimers Dis | 2008 | 18 | **0,47** | 2 | 0,5 | 9 | 0,53 | 5 | 0,45 | 1 | 0,33 | 1 | 0,33 |
| 22 | Porsteinsson | Curr Alzheimer Res | 2008 | 20 | **0,53** | 2 | 0,5 | 10 | 0,59 | 6 | 0,55 | 1 | 0,33 | 1 | 0,33 |
| 21 | Schmidt | J Neurol Neurosurg Psychiatry | 2008 | 13 | **0,34** | 1 | 0,25 | 7 | 0,41 | 3 | 0,27 | 1 | 0,33 | 1 | 0,33 |
| 20 | Levin | Neurosci Behav Physiol | 2009 | 4 | **0,11** | 1 | 0,25 | 1 | 0,06 | 0 | 0 | 2 | 0,67 | 0 | 0 |
| 19 | Aarsland | Lancet Neurol | 2009 | 22 | **0,58** | 3 | 0,75 | 9 | 0,53 | 6 | 0,55 | 3 | 1 | 1 | 0,33 |
| 18 | Modrego | Eur J Neurol | 2010 | 16 | **0,42** | 3 | 0,75 | 5 | 0,29 | 5 | 0,45 | 2 | 0,67 | 1 | 0,33 |
| 17 | Emre | Lancet Neurol | 2010 | 23 | **0,61** | 2 | 0,5 | 11 | 0,65 | 5 | 0,45 | 3 | 1 | 2 | 0,67 |
| 16 | Vercelletto | J Alzheimers Dis | 2011 | 26 | **0,68** | 2 | 0,5 | 12 | 0,71 | 7 | 0,64 | 3 | 1 | 2 | 0,67 |
| 15 | Ashford | J Alzheimers Dis | 2011 | 5 | **0,13** | 2 | 0,5 | 0 | 0 | 2 | 0,18 | 0 | 0 | 1 | 0,33 |
| 14 | Choi | Curr Med Res Opin | 2011 | 16 | **0,42** | 3 | 0,75 | 4 | 0,24 | 5 | 0,45 | 2 | 0,67 | 2 | 0,67 |
| 13 | Fox | PLoS One | 2012 | 24 | **0,63** | 3 | 0,75 | 8 | 0,47 | 7 | 0,64 | 3 | 1 | 3 | 1 |
| 12 | Saxton | J Alzheimers Dis | 2012 | 20 | **0,53** | 3 | 0,75 | 8 | 0,47 | 6 | 0,55 | 2 | 0,67 | 1 | 0,33 |
| 11 | Wilkinson | J Alzheimers Dis | 2012 | 25 | **0,66** | 3 | 0,75 | 12 | 0,71 | 7 | 0,64 | 3 | 1 | 0 | 0 |
| 10 | Hanney | Lancet | 2012 | 28 | **0,74** | 4 | 1 | 14 | 0,82 | 7 | 0,64 | 2 | 0,67 | 1 | 0,33 |
| 9 | Howard | N Engl J Med | 2012 | 22 | **0,58** | 2 | 0,5 | 11 | 0,65 | 7 | 0,64 | 0 | 0 | 2 | 0,67 |
| 8 | Boxer | Lancet Neurol | 2013 | 24 | **0,63** | 3 | 0,75 | 10 | 0,59 | 7 | 0,64 | 2 | 0,67 | 2 | 0,67 |
| 7 | Herrmann | Int Psychogeriatr | 2013 | 21 | **0,55** | 2 | 0,5 | 10 | 0,59 | 6 | 0,55 | 2 | 0,67 | 1 | 0,33 |
| 6 | Grossberg | CNS Drugs | 2013 | 24 | **0,63** | 3 | 0,75 | 11 | 0,65 | 6 | 0,55 | 3 | 1 | 1 | 0,33 |
| 5 | Wang | J Clin Psychopharmacol | 2013 | 10 | **0,26** | 2 | 0,5 | 2 | 0,12 | 3 | 0,27 | 2 | 0,67 | 1 | 0,33 |
| 4 | Dysken | JAMA | 2014 | 21 | **0,55** | 2 | 0,5 | 7 | 0,41 | 8 | 0,73 | 2 | 0,67 | 2 | 0,67 |
| 3 | Cumbo | J Alzheimers Dis | 2014 | 14 | **0,37** | 3 | 0,75 | 4 | 0,24 | 4 | 0,36 | 3 | 1 | 0 | 0 |
| 2 | Araki | Int J Geriatr Psychiatry | 2014 | 12 | **0,32** | 2 | 0,5 | 4 | 0,24 | 4 | 0,36 | 2 | 0,67 | 0 | 0 |
| 1 | Ballard | J Am Med Dir Assoc | 2015 | 24 | **0,63** | 3 | 0,75 | 11 | 0,65 | 7 | 0,64 | 1 | 0,33 | 2 | 0,67 |
| | | | **mean** | | **0,475** | | 0,592 | | 0,442 | | 0,479 | | 0,612 | | 0,355 |
| | | | **95% CI -UL** | | 0,415 | | 0,520 | | 0,362 | | 0,420 | | 0,502 | | 0,258 |
| | | | **95% CI -LL** | | 0,534 | | 0,663 | | 0,520 | | 0,538 | | 0,720 | | 0,453 |
| | | | **median** | | **0,515** | | 0,500 | | 0,470 | | 0,500 | | 0,670 | | 0,330 |

**Table 2.** *CONSORT compliance per article*

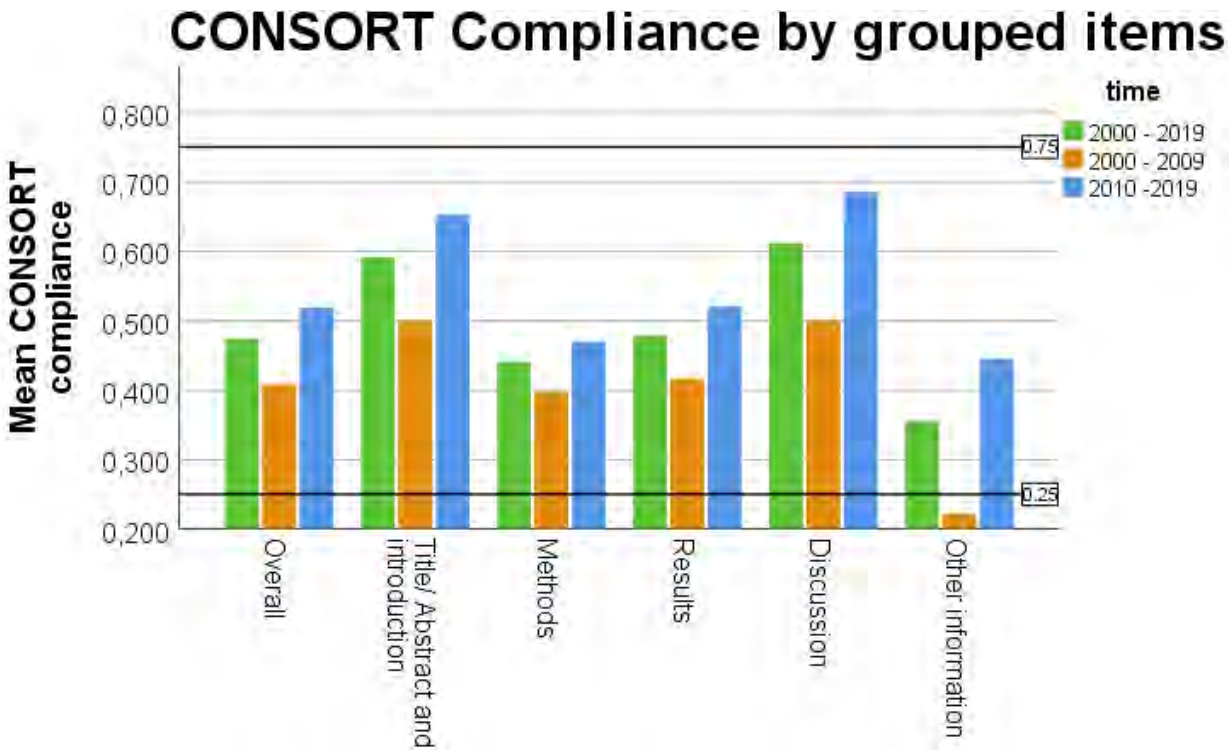


**Figure 2.** *Clustered Bar Chart of CONSORT compliance by group of items, separated in time periods*

The percentage of RCTs with "Greater than 75% overall compliance" was 0% and the percentages of RCTs with "Greater than 75% compliance per group of items" were 47% (Title /Abstract and Introduction), 3% (Methods), 0% (Results), 23% (Discussion), and 3% (Other Information), respectively. The results can be seen in Table 3.

| | Greater than 75% CONSORT compliance | | | | | |
|---|---|---|---|---|---|---|
| | Overall | Title/Abstract and Intro | Methods | Results | Discussion | Other information |
| **RCTs percentage** | **0** | **0,47** | **0,03** | **0,00** | **0,23** | **0,03** |

**Table 3.** *Greater than 75% compliance, expressed as Mean RCTs percentage*

Regarding the "Overall CONSORT compliance" among the different categories of articles, the Median scores of article published in first (2000 – 2009) or second period (2010 – 2019) were 41% and 57% respectively. These percentages were found to be significantly different (Mann – Whitney U, $p = 0.027$). The Median scores of articles published in low ($IF < 3$), medium ($3 \leq IF < 7$), and high ($IF \geq 7$) Impact Factor ranked journals were 42%, 49% and 49% respectively. These percentages were not found to be significantly different (Kruskal - Wallis, $p = 0.233$). The Median scores of articles published in the group of journals which are not currently CONSORT endorsers or the group of journals which are currently CONSORT endorsers were 47% and 58% respectively. These percentages were not found to be significantly different (Mann – Whitney U, $p = 0.425$). The Median scores of articles published in small ($n < 30$), medium ($30 \leq n < 100$), and large ($n \geq 100$) trials were 13%, 50% and 53% respectively. These percentages were found to be significantly different (Kruskal - Wallis, $p = 0.019$). All the above mentioned results can be seen in the table 4.

| | | Overall CONSORT compliance | | | |
|---|---|---|---|---|---|
| | | mean | median | | |
| **Publication Period** | 2000-2009 | 0,41 | 0,41 | **Mann - Whitney U** | |
| | 2010-2019 | 0,52 | 0,57 | **p - value** | **0,027** |
| **Impact Factor** | low(IF<3) | 0,40 | 0,42 | **Kruskal - Wallis** | |
| | medium (IF 3-7) | 0,47 | 0,49 | **p - value** | 0,233 |
| | high (IF>7) | 0,55 | 0,49 | | |
| **CONSORT endorsement** | NO | 0,45 | 0,47 | **Mann - Whitney U** | |
| | YES | 0,51 | 0,58 | **p - value** | 0,425 |
| **Trial size** | small (n<30) | 0,17 | 0,13 | **Kruskal - Wallis** | |
| | medium (n = 30 -100) | 0,50 | 0,50 | **p - value** | **0,019** |
| | large (n >100) | 0,51 | 0,53 | | |

**Table 4.** *Overall CONSORT compliance per different category*

At last, the "Item CONSORT compliance" per publication time periods can be seen in Table 5. Apart from the already mentioned 5 non – applicable items (3b, 6b, 7b, 14b, 17b), we can also see that 6 out of 38 items (15.79%) were under-reported, meaning reported in less than 25% of RCTs in the total period:

- Item 1b (Structured summary) Mean CONSORT compliance 3% (2000 – 2019), 0% (2000 – 2009), 6% (2010 - 2019).
- Item 4b (Settings and locations) Mean CONSORT compliance 20% (2000 – 2019), 0% (2000 – 2009), 33% (2010 -2019).
- Item 10 (Implementation) Mean CONSORT compliance 10% (2000 – 2019), 0% (2000 – 2009), 17% (2010 - 2019).
- Item 14a (Recruitment and follow-up dates) Mean CONSORT compliance 3% (2000 – 2019), 0% (2000 – 2009), 6% (2010 -2019).
- Item 19 (Harms) Mean CONSORT compliance 0% (2000 – 2019), 0% (2000 – 2009), 0% (2010 -2019).
- Item 24 (Protocol) Mean CONSORT compliance 7% (2000 – 2019), 0% (2000 – 2009), 11% (2010 -2019).

On the other hand, only 10 out of 38 items (26.3%) were reported in more than 75% of RCTs in the total period (2a, 4a, 6a, 12a, 13, 13a, 13b, 15, 16, 22).

| Data<br>Item | 2000 - 2019<br>(n =30) | 2000 - 2009<br>(n =12) | 2010 - 2019<br>(n =18) |
|---|---|---|---|
| **Abstract/Title** | | | |
| item1a | 0,73 | 0,67 | 0,78 |
| item1b | 0,03 | 0,00 | 0,06 |
| **Introduction** | | | |
| item2a | 1,00 | 1,00 | 1,00 |
| item2b | 0,60 | 0,33 | 0,78 |
| **Methods** | | | |
| item3a | 0,43 | 0,17 | 0,61 |
| item3b | 0,03 | 0,00 | 0,06 |
| item4a | 0,87 | 0,92 | 0,83 |
| item4b | 0,20 | 0,00 | 0,33 |
| item5 | 0,63 | 0,67 | 0,61 |
| item6a | 0,80 | 0,83 | 0,78 |
| item6b | 0,03 | 0,00 | 0,06 |
| item7a | 0,73 | 0,67 | 0,78 |
| item7b | 0,03 | 0,08 | 0,00 |
| item8a | 0,50 | 0,42 | 0,56 |
| item8b | 0,47 | 0,50 | 0,44 |
| item9 | 0,33 | 0,17 | 0,44 |
| item10 | 0,10 | 0,00 | 0,17 |
| item11a | 0,37 | 0,33 | 0,39 |
| item11b | 0,57 | 0,58 | 0,56 |
| item12a | 0,90 | 0,92 | 0,89 |
| item12b | 0,50 | 0,50 | 0,50 |
| **Results** | | | |
| item13 | 0,77 | 0,58 | 0,89 |
| item13a | 0,93 | 0,92 | 0,94 |
| item13b | 0,87 | 0,83 | 0,89 |
| item14a | 0,03 | 0,00 | 0,06 |
| item14b | 0,00 | 0,00 | 0,00 |
| item15 | 0,90 | 0,83 | 0,94 |
| item16 | 0,80 | 0,67 | 0,89 |
| item17a | 0,57 | 0,42 | 0,67 |
| item17b | 0,00 | 0,00 | 0,00 |
| item18 | 0,40 | 0,33 | 0,44 |
| item19 | 0,00 | 0,00 | 0,00 |
| **Discussion** | | | |
| item20 | 0,67 | 0,42 | 0,83 |
| item21 | 0,30 | 0,17 | 0,39 |
| item22 | 0,87 | 0,92 | 0,83 |
| **Other information** | | | |
| item23 | 0,33 | 0,00 | 0,56 |
| item24 | 0,07 | 0,00 | 0,11 |
| item25 | 0,67 | 0,67 | 0,67 |

**Table 5**. *Item CONSORT compliance, by time periods, expressed as percentage of RCTs reporting the item*

## 5. CONCLUSION

The main conclusion of this study is that the reporting quality of RCTs for Memantine treatment in Dementia published from 2000 to 2019 is far from optimal. Additionally, this study offers a general view of Memantine RCTs, grouped in different categories.

The Mean and Median "Overall CONSORT compliance" were only 47.5% (41.5% - 53.4%) and 51.5% respectively. The percentage of RCTs with "Greater than 75% overall compliance" was 0%. There were 6 out of 38 (15.79%) under-

reported items (reported in less than 75% of RCTs): 1b, 4b, 10, 14a, 19, 24. All these results provide a strong evidence of huge gaps in reports of critical information regarding the RCTs.

We must admit that some of the items were usually justifiably non-applicable (3b, 6b, 7b, 14b, 17b). On the other hand, some critical items (1b – Structured summary, 19 – Harms) were completely null, despite of being very important. Most of the readers due to time and access limitations use only abstracts and, additionally one of the most crucial points we need to consider before making a decision to implement a therapy is the risk of adverse events[17, 18]. We must note here that these specific numbers derived from the strict evaluation procedure in compliance with the CONSORT recommended specific extensions for Abstracts and Harms respectively (as specified in the CONSORT 2010 checklist). The results regarding item 1b were negative, because, although most of the articles reported most of the sub-items, some specific sub-items (randomization, masking, registration) were systematically missing. Similarly, regarding item 19, although most of the articles reported harms in general, none of them reported harms which had very low frequency and none of them reported separately patients who had multiple adverse events.

Making comparisons between articles published before and after revision of CONSORT statement in 2010, we saw that there was a significant improvement. The Median "Overall CONSORT compliance" was 41% in first period (2000 – 2009) and 57% in second period (2010 – 2019), (Mann – Whitney U, $p = 0.027$). Significant differences between categories of RCTs grouped by the number of randomized participants (n) were found. The results of median scores were 13%, 50% and 53%, for small ($n < 30$), medium ($30 \leq n < 100$), and large ($n \geq 100$) trials respectively (Kruskal - Wallis, $p = 0.019$). Based on these results, we could claim that the revision of CONSORT statement, as well as the conduct of bigger trials, is related with improved quality of RCTs reports.

On the other hand, the current Journal Impact Factor and the journal's current CONSORT endorsement were not linked with improved reporting quality, as the differences between these groups were not significant. The Median scores in low ($IF < 3$), medium ($3 \leq IF < 7$), and high ($IF \geq 7$) Impact Factor ranked journals were 42%, 49% and 49%, respectively (Kruskal - Wallis, $p = 0.233$), and the Median scores of CONSORT endorsers and CONSORT non- endorsers were 47% and 58% respectively (Mann – Whitney U, $p = 0.425$). These results could seem to be in some way embarrassing because we could conclude that maybe the Editors have not really connected the quality of their journals and the CONSORT endorsement yet with actual implement of CONSORT guidelines.

Regarding the different items of the CONSORT checklist, grouped in semantic categories, the percentages of RCTs with "Greater than 75% compliance per group of items" were 47% (Title /Abstract and Introduction), 3% (Methods), 0% (Results), 23% (Discussion), and 3% (Other Information), respectively. Additionally, the Mean "CONSORT compliance per group of items" was respectively as follows: 59.2% (Title /Abstract and Introduction), 44.2% (Methods), 47.9% (Results), 61.2% (Discussion), 35.5% (Other Information). Based on these numbers, we could claim that the problem of sub-optimal reporting referred in every part of the RCTs article.

The above mentioned results are quite similar to other comparable studies[11, 13]. In 2019, Rikos et al.[16] in their study regarding RCTs in Restless Legs Syndrome found that the mean overall CONSORT compliance was 56.6%. In 2002, Huwiler – Müntener et al.[10] in their study regarding RCTs in general, found that the median score of CONSORT compliance was 12.5 in a 25-item scale. Special attention we should give to studies addressing the problem of suboptimal reporting of specific items regarding Abstracts[17, 19], Allocation concealment method, Implementation[20, 21] and Harms [22]. More specifically, in 2018, Baulig et al.[19] in their study regarding RCTs abstracts on age – related- macular degeneration health care, found that none of the 136 selected abstracts reported all 16 sub-items. Contrary to our study, other authors evaluated the items regarding Structured summary and Harms more positively[13, 16], probably adopting a more liberal implementation of CONSORT guidelines.

The conclusions could be cautiously generalized for other RCTs of drug therapies for different diseases. On the one hand, this study refers to an extent number of articles (n=30), published in different time periods in a variety of medical journals, regarding RCTs for a commonly prescribed top drug (Memantine) treatment in a global widespread disease (Dementia), including 7,321 participants in total. The results are in general compliant to other similar studies. The strength of this review was the thorough implementation of CONSORT 2010 checklist (and specially the extensions for Abstracts and Harms) to the letter. On the other hand, we have to declare that there are important limitations to the interpretation of our study. First of all, the whole evaluation procedure was performed only by one person. We must keep in mind that most of the items and sub-items are not clear enough for anyone to give a simple 'YES' or 'NO' response regarding compliance to CONSORT statement. Moreover, the evaluator was not blind to authors, journal and publication period of each article (reader's bias). It is obvious that subjectivity is a very weak point of our study. Another limitation is that we used the 2010 revision of CONSORT statement for all the articles, independently from the publication period. Finally, we must say that the CONSORT checklist was not designed to be an evaluation tool. On the contrary, this checklist was designed to have a supportive guiding role for authors and editors.

The general feeling is that the RCTs regarding Memantine treatment in Dementia are not adequately reported. We assume that the great ambitions for writing and publishing a clinical study, combined with the urgent need to find a therapy for Dementia may have led to sub-optimal quality reporting. Miscommunication of scientific information is a huge waste. Scientists (as well as Artificial Intelligence machines[23]) need clear, detailed and transparent articles. All the information described by each one of the CONSORT items is important for Researchers, Biomedical Industry and Authorities. Developers of reporting guidelines, editors, authors and funders should collaborate with each other to standardize the RCTs reports[13, 24]. Finally, we strongly believe that the actual implementation of CONSORT statement will decisively improve the reporting quality of articles for the benefit of the whole scientific community and society.

## 6. REFERENCES


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## 7. APPENDIX A – CONSORT checklist

| | | | |
|---|---|---|---|
| **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 | Specific objectives or hypotheses | |
| **Methods** | | | |
| Trial design | 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 | |
| Sample size | 7a | How sample size was determined | |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | |
| Allocation concealment mechanism | 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 | |
| Statistical methods | 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 | |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | |
| Numbers analysed | 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 | — |
| Ancillary analyses | 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 | |

## 8. APPENDIX B - List of articles included in the analysis (*sorted by the most recent*).


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## 9. **APPENDIX C** – Analytical Results *(CONSORT checklist: 0 = NO, 1= YES)*

| RCT - item | RCT 30 | RCT 29 | RCT 28 | RCT 27 | RCT 26 | RCT 25 | RCT 24 | RCT 23 | RCT 22 | RCT 21 | RCT 20 | RCT 19 | RCT 18 | RCT 17 | RCT 16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| item1a | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 |
| item1b | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| item2a | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| item2b | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 |
| item3a | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 |
| item3b | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| item4a | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 |
| item4b | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| item5 | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 |
| item6a | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 1 |
| item6b | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| item7a | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 |
| item7b | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| item8a | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 1 |
| item8b | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 |
| item9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 1 |
| item10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| item11a | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 1 | 1 |
| item11b | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 |
| item12a | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| item12b | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| item13 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 |
| item13a | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 |
| item13b | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 |
| item14a | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| item14b | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| item15 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 |
| item16 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 |
| item17a | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 1 | 1 |
| item17b | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| item18 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| item19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| item20 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 |
| item21 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 |
| item22 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 |
| item23 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| item24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| item25 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 |

| RCT - item | RCT 15 | RCT 14 | RCT 13 | RCT 12 | RCT 11 | RCT 10 | RCT 9 | RCT 8 | RCT 7 | RCT 6 | RCT 5 | RCT 4 | RCT 3 | RCT 2 | RCT 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| item1a | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 |
| item1b | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| item2a | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| item2b | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 1 |
| item3a | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 0 |
| item3b | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| item4a | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 |
| item4b | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 1 |
| item5 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 1 |
| item6a | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 |
| item6b | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| item7a | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 1 |
| item7b | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| item8a | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| item8b | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| item9 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| item10 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| item11a | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| item11b | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 |
| item12a | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 |
| item12b | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 1 |
| item13 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 |
| item13a | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| item13b | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 |
| item14a | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| item14b | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| item15 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 |
| item16 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 |
| item17a | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 1 |
| item17b | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| item18 | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| item19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| item20 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |
| item21 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 0 |
| item22 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 |
| item23 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 1 |
| item24 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| item25 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 1 |