Are older adults insufficiently included in clinical trials?-An umbrella review

Florisson, Sandra; Aagesen, Emilie Kørschen; Bertelsen, Ann Sophia; Nielsen, Lars Peter; Rosholm, Jens-Ulrik

Published in:
Basic & Clinical Pharmacology & Toxicology

DOI:
10.1111/bcpt.13536

Publication date:
2021

Document version:
Accepted manuscript

Citation for pulished version (APA):
Florisson, S., Aagesen, E. K., Bertelsen, A. S., Nielsen, L. P., & Rosholm, J-U. (2021). Are older adults insufficiently included in clinical trials?-An umbrella review. *Basic & Clinical Pharmacology & Toxicology*, *128*(2), 213-223. https://doi.org/10.1111/bcpt.13536

MISS SANDRA FLORISSON (Orcid ID : 0000-0002-6314-4584)

Article type : Mini-Review

MINI REVIEW:

Are older adults insufficiently included in clinical trials? – an umbrella review

- Inclusion of older adults in clinical trials

Co-authorship:

Sandra Florisson[1,2]

Emilie Kørschen Aagesen[1,2]

Ann Sophia Bertelsen[1]

sandraflorisson@gmail.com
mille.1402@hotmail.com

[1]Geriatric Research Unit, Department of Geriatric Medicine, Odense University Hospital, Odense, Denmark
[2] Department of Clinical Research, University of Southern Denmark, Odense, Denmark

Lars Peter Nielsen[3,4]
Jens-Ulrik Rosholm[1,2]

Review - clinical trials – inclusion of older adults – barriers – solutions

Abstract

Treatment guidelines are primarily based on randomized clinical trials (RCTs). RCTs tend to some extent to exclude older adults despite the fact that physicians need guidance when treating this patient group.

By summarizing existing literature, we aimed to: 1) Quantify the proportion of RCTs and other clinical studies (CTs) that did not adequately include older adults; 2) identify the main barriers for this non-inclusion and 3) identify suggested solution for inclusion of older adults in RCTs and other CTs.

[3] Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus, Denmark
[4] Institute of Biomedicine, Aarhus University, Aarhus, Denmark

In this umbrella review, Embase and PubMed were searched for relevant papers, and 2,701 papers were identified. The subsequent screening resulted in 22 papers. The Critical Appraisal Skills Program was used as quality assessment tool to evaluate these 22 papers.

We found that: 1) The most frequent outcome designating missing inclusion of older adults was the use of age limit as exclusion criterion in studies – the proportion of this was 10-60%; 2) barriers for inclusion were mainly exclusion criteria, logistic challenges and financial constraints and 3) more extensive inclusion would require more explicit inclusion criteria, merely application of exclusion criteria when absolutely needed, change of researchers' attitude, further inclusion of supporting relatives to overcome the logistical challenges and more financial funding.

Introduction

Older adults are the most rapidly increasing age group globally (1). 55 to 95% of older adults are categorized as multimorbid and the prevalence is increasing with age (2). Thus, older adults tend to receive more medical treatment compared to younger people (3). Treatment guidelines are primarily based on data from randomized clinical trials (RCTs) (4) that tend to some extent to exclude older adults. The insufficient inclusion of older adults is reflected by a lower external validity in RCTs, where the average age, level of function, comorbidities and number of prescribed drugs do not reflect the target population (5).

Using data from RCTs not including older adults sufficiently is problematic since the age-related physiological changes are not taken into account (6). For instance, evidence supports warfarin inhibition of clotting factors is more efficiently at the same plasma concentration in older adults compared to younger ones (7, 8). Treatment guidelines are often based on chronological age, but physiological changes, i.e., pharmacodynamics and -kinetics, are not uniformly within age groups. The changes cause heterogeneity within age groups and complicate treatment decisions (6).

To our knowledge, the lack of inclusion of older adult is a broad topic, where extent, barriers and solution have not been sufficiently explored and compared. That was the motivation for this study.

Objectives

By summarizing existing literature, the aim of this umbrella review was to: 1) Quantify the proportion of RCTs and other clinical studies (CTs) that did not adequately include older adults; 2) identify the main barriers for this non-inclusion and 3) identify suggested solution for more extensive inclusion of older adults in RCTs and other CTs.

Methods

Study design

This study is an umbrella literature review. The aim of such is to provide an overview of a topic and the study is based primarily on systematic reviews. By summarizing several reviews, consensus and contrasts among the existing literature will be highlighted and possible reasons for these findings will be explored. Therefore, the search will not include predefined outcomes, which is reflected in the search string. An umbrella review can contain both qualitative and quantitative evidence as in the present study (9).

Definitions

In this study, older adults were defined as persons being 65 years or older. This study will refer to both RCTs and CTs under the common term 'CTs' unless otherwise specified.

Data extraction

The inclusion of papers was divided into six consecutive stages: 1) Identification of papers; 2) removal of duplicates; 3) screening of title, abstract and introductory sections; 4) review and final inclusion; 5) The Critical Appraisal Skills Program (CASP) assessment of papers and 6) extraction of relevant data (Figure 1). Endnote (Clarivate, Philadelphia, US) was used for removal of duplicates. All identified papers were quality-assessed and extracted for relevant data independently by the two main authors. Papers not immediately agreed upon were discussed until agreement was reached.

Cohens Kappa coefficient (κ-coefficient) was used to measure agreement between the two authors in the first five stages. Values ranging 61 to 80% was considered good, whereas consensus exceeding 80% was considered almost perfect.

Data search

Literature research was done on 28 February 2020 in PubMed and Embase. Keywords and Medical Subject Headings (MeSH) were searched in PubMed. Keywords and Embase Subject Headings (Emtree) were searched in Embase.

Search strategy and selection criteria

The search string was based on the SPIDER model (10) (see appendix). The SPIDER model is a tool developed for qualitative research questions and consists of five blocks. In this study, they were:

- Sample (S): Older adults.
- Phenomena of Interest (PI): Inadequate inclusion of older adults in RCT and CTs.
- Design (D): RCT and CT.
- Evaluation (E): -.
- Research (R): Literature review.

'Evaluation' was not applied in the search string due to the nature of the umbrella study.

The inclusion criteria were literature reviews of CTs published during the period from January 1990 to February 2020 in English or Danish. This study only focused on drug treatments. Reviews focusing exclusively on surgical and non-medical interventions and psychiatric diseases were excluded, since other barriers could interfere with the non-inclusion. One such example could be an increased risk of drug-related side effects in psychiatric patients (e.g. sedation, anticholinergic effect, cognitive impairment, weight gain). Another example could be ethics of including psychiatric patients (e.g. lack of medical compliance and high dropout rates). Additionally, reviews focusing on diseases and treatments primarily affecting older adults, e.g. dementia, were excluded, as any barriers of inclusion would be of a different nature enabling possible bias (11).

Quality assessment

Initially, two recognised assessment tools were tested prior to use: A MeaSurement Tool to

Assess systematic Reviews (AMSTER) and CASP (12). CASP were assessed as more accurate and was chosen as the final assessment tool.

CASP is based on a checklist of 10 questions which can be answered with "yes", "no" or "can't tell". In this study, the two authors categorised the included papers as being of "low", "medium" or "high" quality depending on the number of "yes" collected (1-4: Low, 5-7: Medium and 8-10: High).

Findings

Initially, 2,701 papers were identified by the literature search (Figure 1). The subsequent screening rendered 22 papers (Table 1, online appendix). Cohen's Kappa coefficient for the final assessment was 97.6%. The 22 papers were assessed according to CASP.

All 22 papers were written in English and published between 2003 and 2018 with a single exception from 1992 (8). Eleven of the papers were systematic reviews and 11 non-systematic reviews. Twelve papers compared RCTs, 9 papers compared CTs and one paper compared CT protocols (13). Ten papers applied one source of data and in general the number of data sources varied between one and six. The most frequently used data source was Medline. In addition, a wide range of sources have been used, including textbooks and Clinical Trials Registry Platforms. The majority of studies addressed pharmacological interventions for various specific disease units, most often cardiology, oncology or haematology (Table 1, online appendix).

The number of included studies in the papers varied between 9 and 4,341. Three studies did not comment on the number of included studies.

Quality assessment of included reviews

According to the CASP assessment, 6 papers were of high quality, 9 papers of medium quality and 7 papers of low quality (Table 1, online appendix).

Five high-quality papers and 5 medium-quality papers were systematic literature reviews comparing RTCs. Low quality papers were mostly characterized by inadequate or missing method sections.

Quantitative results

To quantify the lack of inclusion, the most frequent outcomes in included papers designating missing inclusion of older adults were examined/quantified. These were:

- Studies using age limit as an exclusion criterion.
- Studies using criteria that might disproportionally exclude older adults.
- Age difference between study group and target population.

Several other outcomes were presented? in the included papers (Table 2 and 3).

Only papers of high and medium quality answer this part of the research question, since the papers of low quality either did not answer this or the findings were vaguely validated.

Age limit as an exclusion criterion

Five high-quality papers calculated the percentage of studies using age limit as an exclusion criterion (5, 14-17). This percentage ranged from 10 to 44%. Five medium quality papers found a range between 19 and 60% (8, 13, 18-20).

Two papers found that age limit as an exclusion criterion did not lower the average age of a study population compared to studies that did not use an age limit (14, 17).

Exclusion criteria that might disproportionally exclude older adults

A total of 7 papers quantified and/or discussed the proportion of studies using exclusion criteria that might exclude older adults from CTs. 44 to 83% of studies used exclusion criteria that might disproportionally exclude older adults (5, 15-19, 21). A study on missing inclusion of older adults in CTs concerning antiepileptic medication, examined how different exclusion criteria affected the average age in a study population. The only exclusion criterion that lowered average age in a population was found to be patients with neurological conditions (16). Despite investigator presumptions, this was not the case for other exclusion criteria, e.g. age limit, comorbidity, lesser functional abilities and organ dysfunction.

Age difference

Three papers presented the difference in mean age between the study population and the given target population (15, 21, 22). They found the average study population was 7-10 years younger compared to the target population.

Qualitative results

Barriers identified in included papers

Barriers of inclusion can be divided into three categories: 1) The researcher; 2) the physician and 3) the older adult. Results are shown in table 4.

Solutions identified in included papers

Solutions identified by papers for including older adults fall in the same three categories: 1) The researcher; 2) the physician and 3) the older adult. This is presented in the next section.

The researcher

A total of eight papers suggested solutions for improved inclusion.

Exclusion criteria that might disproportionately exclude older adults must be applied more restrictively and be accurately explained (19, 20, 23-25). In addition, the criteria should be minimized for use only where there is an absolute contraindication for a given intervention.
The same applies to the use of age as an exclusion criterion (13, 19, 20, 23, 26, 27). Inclusion criteria need to be presented more explicitly in the protocol to help the physician overcome any hesitation of including older adults (19). One paper encouraged to focus more on the external validity when making protocols for new CTs (20).

Relevant study outcomes, e.g. pharmacodynamics and -kinetics, should be more in focus in CTs. This is pointed out by two papers (23, 28). Three papers suggest that more studies should be performed exclusively in older adults (19, 25).

Study information must be understandable and accessible for the older adults (e.g. read by a nurse, plain language and larger front size) (24, 26-29).

One paper mentioned the relevance of follow-on older adults to ensure treatment does not cease after completion of the study (26). This will ensure older adults to feel safe and ensure that their treatment continue after the trail ends.

Commented [HH1]: Should this be "follow-up"?

The importance of a constant trial team is emphasized by two papers (27, 28). This might solve any uncertainty and, in addition, provide an accessible treatment team with the necessary skills.

New ways of communication, e.g. media, posters and flyers, could improve recruitment of older adults (24, 28).

Four papers mentioned chronological age as an insufficient indicator when assessing older adults, whereas geriatric assessment tools could be a relevant alternative (19, 23, 24, 30). However, at present available assessment tools are unable to accurately classify older adults, and two papers suggested development of an improved tool (27, 29).

The physician and the older adult

Six papers proposed logistic help, e.g. transportation including financial compensation, since this is a major obstacle to participation of the older adult (24, 26-28, 30, 31). Furthermore, trials should focus more on convenience to the older adults, e.g. consultations at home (27). Inclusion of supporting relatives is also important in several aspects, which was mentioned in two papers (28) (24). In particular, it emphasizes the significance of overcoming communicative barriers, as relatives can promote the process of understanding and remembering information. In addition, they can provide support during a given intervention and provide transportation.

One paper called for a focus group interview to clarify the perspective of older adults on participation in clinical studies, since this has not been examined thoroughly (28). In addition, it was encouraged to study outcomes relevant to older adults, such as quality of life, improved functional abilities and pain relief (18). The nature of outcomes is likely to increase motivation

for participation. Five papers mentioned time and more resources as contributory to better communication between physician and older adults. This would ensure that older adults make the decision to participate on an informed basis and understand the importance of participating in clinical trials (19, 23, 24, 28, 29).

Discussion

Age limit as exclusion criterion

In this study, the most frequently used outcome designating missing inclusion of older adults is age as exclusion criterion. The tendency to use age limit as an exclusion criterion has been slightly decreasing over time (16, 20), but a trend for increasing mean age in clinical studies has not so far been observed (14, 32). Since 1993, international guidelines have recommended not to exclude persons only based on an age limit (17). Nonetheless, age limit has been used extensively until 2005-2010 (14, 17). If an age limit has been used since then, there is a tendency towards a higher age limit than 65 years compared to previously (13, 14). However, the mean age in clinical studies is found by several papers to be independent of age as an exclusion criterion (14, 16, 17). Consequently, other factors that similarly lower the average age of older adults in the studies have replaced the influence of an age limit.

Exclusion criteria which might disproportionately exclude older adults

Seven of the included papers stated that the use of certain exclusion criteria disproportionately excluded older adults (5, 15-19, 21). The association between a given exclusion criterion and lack of inclusion of older adults is mostly presented without evidence. Criteria quantified in included papers were often based on assumptions about impact of individual criteria on study population and external validity. It is difficult to determine the extent to which older adults were excluded from participating without knowing the prevalence of a given condition used as exclusion

criterion. Therefore, it is unclear whether application of such exclusion criteria can be used as a precise surrogate measure on sufficient inclusion of older adults in CTs.

Exclusion criteria most frequently applied were: Comorbidity (23, 25); severe geriatric illnesses (5) and decreased level of functioning in everyday life (23). These will often rule out an unknown, but presumably high, proportion of older adults. It is a fact that the prevalence of many diseases increases with age. Therefore, a quantification of studies with such exclusion criteria could be an easily accessible way to clarify missing inclusion of older adults. At present, this might be the most realistic method to quantify the extent of the problem, as a precise calculation of each criterion's impact in a study group will be difficult or even impossible.

Theoretically, if the presence of these criteria is accepted as a surrogate measure for lack of inclusion, another problem will arise. There was no consensus between papers as to which criteria might cause a disproportionate exclusion of older adults and no consensus on how to categorize these. In some papers, exclusion criteria are categorized as disease units, e.g. heart diseases or endocrine diseases, whereas others are categorized individually, e.g. MI, heart failure, essential hypertension. As each paper used different criteria with different categorization, a comparison across criteria was impeded. Therefore, the proportion of studies with exclusion criteria that might disproportionately exclude older adults is not quantified per disease unit but presented for all categories in this study.

Identified barriers

The majority of barriers identified are linked to the protocol, mental impairment in older adults and limited financial resources. Other barriers are primarily related to ethical considerations for the researcher and the physician. The ethical challenge focus on desire to achieve the highest possible external validity by including all possible subjects, while at the same time ensuring the proper exclusion of elderly and frail individuals. The ethical consideration requires an exclusion of the most vulnerable patients, in case the expected health outcome of the patient will be worse compared to non-participation.

Physicians' reluctance to include older adults in CTs due to few and broad inclusion criteria is a barrier for enrolling older adults. Such hesitation results from the physicians' subjective attitude to the older adults' health affecting whether he or she is invited to attend. This way, older adults who might be found suitable for participation according to protocol will not be invited. Probably, this is because the physicians feel a responsibility to spare fragile and older adults from recruitment - a responsibility that should otherwise lie with the researcher and should be prevented by a well-executed protocol. An example of this is seen in a clinical setting concerning antithrombotic treatment. Bajorek et al. investigated antithrombotic treatment for patients with atrial fibrillation and found that adults aged 80 years or more were more likely not to receive relevant warfarin treatment compared to individuals less than 80 years old. The primary reason for this was hesitation from physicians due to age (33). Pugh et al. studying the attitude of physicians towards anticoagulation for atrial fibrillation, found physician hesitation to antithrombotic treatment in older adults, even though evidence demonstrated a beneficial treatment effect (34).

A topic that needs further clarification is why older adults, who are invited to clinical trials refuse to participate. Petty et al. investigated this and found: 1) Confusion or lack of understanding of the clinical trial; 2) not feeling healthy enough to attend - this might lead to a selection bias based on health status; 3) distrust and negative attitude towards the health system and/or 4) not finding their own disease status relevant to be examined (35).

Identified solutions

The majority of solutions identified match the barriers in general. Most are linked to the researcher and a more explicit use of inclusion and exclusion criteria. Other solutions emphasise the older adults to feel safer before during and after participating in a trial.

The use of chronological age has been criticised by several papers. These papers suggest the use of a geriatric assessment toll as an alternative. Geriatric assessment tools should divide the heterogeneous elderly population into groups that are more homogeneous and not based on

chronological age. Such groups might consist of fewer individuals and thus the probability of achieving statistically significant results can be reduced.

Another approach could be the use of subgroup analyses. By doing so, results from clinical trials would be transferable to specific groups of older adults. In turn, this will improve external validity and contribute to quality of clinical guidelines.

Consensus among research questions

When looking at the three research questions, it is clear that the quantitative question (the first part of the research question) is only answered by high and medium assessed papers. The focus here is mainly on the protocol, more specific on presence of inclusion and exclusion criteria. If looking only at the papers assessed high and medium, one might have the impression that the lack of inclusion only links to the protocol.

The last two research questions are qualitative and are mainly answered by papers assessed low and medium quality. These papers suggest other factors also have an impact on the lack of inclusion besides the protocol. Here, the focus is mainly on barriers and solutions in three different categories: The researcher, the physician and the older adult. Therefore, inclusion of low, medium and high-quality assessed papers gives a broader perspective on the topic. It opens for new ways of improving inclusion. This transfers some of the responsibility from the researchers to the physician and the older adults, making it a shared responsibility.

Perspectives

Solutions for improving recruitment have been suggested, but most are not easily applicable.

Adams et al. found that the most effective method of recruiting older adults in clinical trials was via their relatives and their own physicians, who recommended the older adults to participate (36). Two papers mentioned connection of older adults to and confidence in their physician (27, 29). In this process, it is important for the physician to consider the ethical aspects since the physician has a duty to offer their patients the best possible treatment, which may not always be

achieved through participation in clinical studies. E.g., if a treatment is suspected of being nephrotoxic, and a great part of older adults have reduced kidney function to some degree, should the physician then invite the older adult to participate and thereby risk a negative outcome, instead of offering the standard treatment?

Harari et al. mentioned the difficulty of enrolling a sufficient number of patients to clinical trials due to strict selection criteria. To overcome this problem, the paper discusses the benefit of real-life studies, in which study populations will reflect the target population to a higher extent, and barriers of recruitment will be reduced significantly. Limitations of real-life studies are also considered and data must be supplied by data from RCTs (37).

Strengths and weaknesses

Selection of studies

In the inclusion of papers, κ- coefficients for the selection process was high (97.6%). This indicates high agreement among the two authors who did the inclusion of the papers.

Design of included studies

Out of the 22 papers, 11 papers were systematic literature reviews. If the study had been based solely on systematic literature studies, validity of our findings would have been higher. But in the initial phase of the study, it was clear there was not a sufficient number of systematic literature reviews available to sufficiently answer the research questions, and literature reviews of lower quality were therefore included. The importance of this involvement is also emphasized by the fact that systematic literature reviews often do not include qualitative studies, which would render the authors unable to answer the qualitative part of the research question.

Time frame

All papers except one were published in 2003 or later. Since the included papers were reviews, the data presented in these studies were collected from previously published CTs. The rather long timespan offered a possibility to see potential time trends of exclusion of older adults.
On the other hand, studies published before the year of 1990 were excluded, however, not assumed to affect the study.

Conclusion

Based on the reviewed literature, it is clear that older adults are not sufficiently included in CTs. There is no trend towards improvement of this problem. This is reflected e.g., by difference in mean age between study population and target population, despite the fact the that application of age limit as exclusion criterion is decreasing. Also, exclusion criteria that might disproportionally exclude older adults are still part of the problem.

The barriers of inclusion of older adults can be considered as three categories: 1) The research protocol with exclusion criteria; 2) the physician, who does not invite older adults sufficiently and 3) the older adults who refuse to participate in CTs. Part of the basis in each category originates from limited financial resources as well as logistic challenges.

This study identified a number of possible solutions from included papers, including more explicit inclusion criteria, less restrictive exclusion criteria and more financial resources. In addition, improved communication between older adults and clinicians could be a way to limit fear and uncertainties.

Conflict of Interest Statement

None.

References

1. Economic NUDoI, Divisiom SAP, Unidas N, Economic UNDo, population NUDdl. World population to 2300: United Nations Publications; 2004.
2. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: a systematic review of the literature. Ageing research reviews. 2011;10(4):430-9.
3. Lernfelt B, Samuelsson O, Skoog I, Landahl S. Changes in drug treatment in the elderly between 1971 and 2000. European journal of clinical pharmacology. 2003;59(8-9):637-44.
4. Garfield FB, Garfield JM. Clinical judgment and clinical practice guidelines. International journal of technology assessment in health care. 2000;16(04):1050-60.
5. Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA. Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. Journal of general internal medicine. 2011;26(7):783-90.
6. Singh S, Bajorek B. Pharmacotherapy in the ageing patient: The impact of age per se (A review). Ageing research reviews. 2015;24(Pt B):99-110.
7. Shepherd AM, Hewick DS, Moreland TA, Stevenson IH. Age as a determinant of sensitivity to warfarin. British journal of clinical pharmacology. 1977;4(3):315-20.
8. Gurwitz JH, Col NF, Avorn J. The exclusion of the elderly and women from clinical trials in acute myocardial infarction. Jama. 1992;268(11):1417-22.
9. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. International Journal of Evidence-Based Healthcare. 2015;13(3):132-40.
10. Methley AM, Campbell S, Chew-Graham C, McNally R, Cheraghi-Sohi S. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. BMC health services research. 2014;14:579.
11. Woodall A, Morgan C, Sloan C, Howard L. Barriers to participation in mental health research: are there specific gender, ethnicity and age related barriers? BMC psychiatry. 2010;10(1):103.
12. Akobeng AK. Principles of evidence based medicine. Archives of disease in childhood. 2005;90(8):837-40.

13. Cruz-Jentoft AJ, Gutierrez B. Upper age limits in studies submitted to a research ethics committee. Aging clinical and experimental research. 2010;22(2):175-8.
14. Dodd KS, Saczynski JS, Zhao Y, Goldberg RJ, Gurwitz JH. Exclusion of older adults and women from recent trials of acute coronary syndromes. Journal of the American Geriatrics Society. 2011;59(3):506-11.
15. Avni T, Shiver-Ofer S, Leibovici L, Tacconelli E, DeAngelis G, Cookson B, et al. Participation of elderly adults in randomized controlled trials addressing antibiotic treatment of pneumonia. Journal of the American Geriatrics Society. 2015;63(2):233-43.
16. Desmarais P, Miville C, Milan-Tomas A, Nguyen QD, Ojeda-Lopez C, Masellis M, et al. Age representation in antiepileptic drug trials: A systematic review and meta-analysis. Epilepsy research. 2018;142:9-15.
17. Gouverneur A, Salvo F, Berdai D, Moore N, Fourrier-Reglat A, Noize P. Inclusion of elderly or frail patients in randomized controlled trials of targeted therapies for the treatment of metastatic colorectal cancer: A systematic review. J Geriatr Oncol. 2018;9(1):15-23.
18. Bellera C, Praud D, Petit-Moneger A, McKelvie-Sebileau P, Soubeyran P, Mathoulin-Pelissier S. Barriers to inclusion of older adults in randomised controlled clinical trials on Non-Hodgkin's lymphoma: A systematic review. Cancer Treatment Reviews. 2013;39(7):812-7.
19. Hamaker ME, Stauder R, van Munster BC. Exclusion of older patients from ongoing clinical trials for hematological malignancies: an evaluation of the National Institutes of Health Clinical Trial Registry. The oncologist. 2014;19(10):1069-75.
20. Thake M, Lowry A. A systematic review of trends in the selective exclusion of older participant from randomised clinical trials. Archives of gerontology and geriatrics. 2017;72:99-102.
21. Hori A, Shibata T, Kami M, Kusumi E, Narimatsu H, Kishi Y, et al. Age disparity between a cancer population and participants in clinical trials submitted as a new drug application of anticancer drugs in Japan. Cancer. 2007;109(12):2541-6.
22. Jennens RR, Giles GG, Fox RM. Increasing underrepresentation of elderly patients with advanced colorectal or non-small-cell lung cancer in chemotherapy trials. Internal medicine journal. 2006;36(4):216-20.
23. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(13):3112-24.

24. Ridda I, MacIntyre CR, Lindley RI, Tan TC. Difficulties in recruiting older people in clinical trials: an examination of barriers and solutions. Vaccine. 2010;28(4):901-6.
25. Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. Trials. 2015;16:495.
26. Bayer A, Fish M. The doctor's duty to the elderly patient in clinical trials. Drugs & aging. 2003;20(15):1087-97.
27. Kazmierska J. Do we protect or discriminate? Representation of senior adults in clinical trials. Reports of practical oncology and radiotherapy : journal of Greatpoland Cancer Center in Poznan and Polish Society of Radiation Oncology. 2012;18(1):6-10.
28. Witham MD, McMurdo ME. How to get older people included in clinical studies. Drugs & aging. 2007;24(3):187-96.
29. Denson AC, Mahipal A. Participation of the elderly population in clinical trials: barriers and solutions. Cancer control : journal of the Moffitt Cancer Center. 2014;21(3):209-14.
30. Vitale C, Fini M, Spoletini I, Lainscak M, Seferovic P, Rosano GM. Under-representation of elderly and women in clinical trials. International journal of cardiology. 2017;232:216-21.
31. Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJ, et al. Participation of patients 65 years of age or older in cancer clinical trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2003;21(7):1383-9.
32. Gouverneur A, Salvo F, Berdai D, Moore N, Fourrier-Reglat A, Noize P. Inclusion of elderly or frail patients in randomized controlled trials of targeted therapies for the treatment of metastatic colorectal cancer: A systematic review. Journal of Geriatric Oncology. 2018;9(1):15-23.
33. Bajorek B, Krass I, Ogle S, Duguid M, Shenfield G. The impact of age on antithrombotic use in elderly patients with non-valvular atrial fibrillation. Australasian Journal on Ageing. 2002;21(1):36-41.
34. Pugh D, Pugh J, Mead GE. Attitudes of physicians regarding anticoagulation for atrial fibrillation: a systematic review. Age and ageing. 2011;40(6):675-83.
35. Petty DR, Zermansky AG, Raynor DK, Vail A, Lowe CJ, Freemantle N, et al. "No thank you": why elderly patients declined to participate in a research study. Pharmacy world & science : PWS. 2001;23(1):22-7.
36. Adams J, Silverman M, Musa D, Peele P. Recruiting older adults for clinical trials. Controlled clinical trials. 1997;18(1):14-26.

37. Harari S. Randomised controlled trials and real-life studies: two answers for one question. European respiratory review : an official journal of the European Respiratory Society. 2018;27(149).
38. Dunn C, Wilson A, Sitas F. Older cancer patients in cancer clinical trials are underrepresented. Systematic literature review of almost 5000 meta- and pooled analyses of phase III randomized trials of survival from breast, prostate and lung cancer. Cancer epidemiology. 2017;51:113-7.

Tables

Table 1: online appendix.

	Systematic literature studies (n)	Includes RCT (n)	Quantitative results of included papers
CASP: HIGH n = 6	5	5	**Avni et al. (15):** Up to 100% of the included studies used age limit or other exclusion criteria* which might disproportionately exclude the older adults. Mean age of participants in the presented RCTs is 54 years, and 66 years in the observational studies, which leaves an age gap of 10 years between the study and target population. **Desmaris et al. (16):** 44% of the identified studies use age as an exclusion criterion. 60% of studies uses comorbidities as exclusion criteria which are suspected of disproportionately exclude the older adults. Over time no significant decrease in the use of age limit was found. When considering all exclusion criteria, only presence of neurological diseases as an exclusion criterion was significantly associated with a reduction of average age of the participants. **Dodd et al. (14):** Nearly 30% of studies have explicit age limits as exclusion criteria. Almost no difference in mean age of participants is found in trials with age-based exclusion compared to studies with no age-based exclusion. No studies evaluate outcomes considered relevant for the older adults **. **Gouverneur et al. (32):** 16,7% of studies use age limits as exclusion criteria. 83,3% exclude patients with CNS metastases and 37% excludes frail patients based on PS-scale***, both criteria which might disproportionately exclude the older adults. In the identified studies patients aged 65 years or older represent 40% compared to 65% in the target population. **Kennedy-Martin et al. (25):** In 71,2% of studies the authors conclude that RCT samples was not representative of the target group. The target group were more likely to be women, older adults or have more comorbidities than the study population. **Zulman et al. (5):** 10,2% of studies use age limits as exclusion criteria. 45,6% uses exclusion criteria* that might disproportionately exclude the older adults. Only 26,6% evaluates outcomes considered relevant for the older adults **.

CASP: MEDIUM n = 9	5	5	**Bellera et al. (18):** 25,3% of studies use age limits as exclusion criteria. 54% uses exclusion criteria which might disproportionately exclude the older adults. Few evaluated outcomes considered relevant for the older adults**. **Cruz-Jentoft et al. (13):** During a period from 1994-2007 the authors found a fall in the tendency to use upper age limit as an exclusion criterion without explanation from 36 to 19%. No increase in number of studies designed specific for older adults in this time period is found. **Dunn et al. (38):** Participants in breast cancer studies is underrepresented from the age of 55 years, and in lung cancer studies from 70 years, compared to cancer incidence from WHO. Participants aged 70 years and older were consistently underrepresented with 12 to 35% less than expected. **Gurwitz et al. (8):** Over 60% had age limits as exclusion criteria and the most frequently used age threshold was 75 years. The mean age of participants in studies with age-based exclusion was 56,8 years compared with 59,2 for studies without such exclusion. Compared to before year 1979 an increase in use of age limit as exclusion criterion is found. **Hamaker et al. (19):** 27% of studies use age limits as exclusion criteria. 74% of studies used reduced kidney function, and 27% used reduced liver function as exclusion criteria. **Hori et al. (21):** 44% use exclusion criteria* that might disproportionately exclude the older adults. The median age of the cancer population was 69 years, giving a median difference in age between CT participants and the cancer population to be 7 years. **Jennens et al. (22):** The median age of patients with cancer is increased through the past decades, without a similar increase in the median age in study populations. The median age difference is about 8 years. The use of age limit as exclusion criterion is decreased from 51% in 1980s to 29% in 1990s. **Thake et al. (20):** 29% of studies use age limits as exclusion criteria. 92,8% did not clarify the reason for this age cut off. Over a period of 18 years a small but statistically significant decrease in the proportion RCTs with unjustified upper age limits was found. **Townsley et al. (23):** 1,3% of cancer patients aged 65-75 years are included in studies and for patients aged 75 or more 0,5% is included. Only $^{1}/_{4}$ to $^{1}/_{3}$ of the potentially eligible older patients

are enrolled in clinical studies. Younger people are to a greater extend invited for the studies: The participation rate for the asked older is similar with the younger ones.

Table 2 - Reasons for non-inclusion of elderly adults in CTs

*Reduced organ function, reduced level of function, comorbidities, polypharmacy, short life expectancy and inability to consent.

**Quality of life, level of function, pain relief and toxicity (5, 18).

***Tool to assess a patient's general health. The scale is from 0-4.

	Age as exclusion criterion	Criteria that might disproportionately exclude	Age difference between study and target group	Others
CASP high				
Avni et al. (15)	X	X	X	
Desmaris et al. (16):	X	X		X
Dodd et al. (14):	X			X
Gouverneur et al. (32):	X	X		X
Kennedy-Martin et al. (25):				X
Zulman et al. (5)	X	X		X
Sum, high	*5*	*4*	*1*	*3*
CASP medium				
Bellera et al. (18):	X	X		X
Cruz-Jentoft et al. (13):	X			X
Dunn et al. (38):				X
Gurwitz et al. (8):	X			X
Hamaker et al. (19):	X	X		
Hori et al. (21):		X	X	X

Jennens et al. (22):			X	
Thake et al. (20):	X			X
Townsley et al. (23):				X
Sum, medium	*5*	*3*	*2*	*6*
Total sum	10	7	3	9

Table 3 – The most frequent outcomes designating missing inclusion of older adults

Performance score (PS)

- A tool to assess a patient's general health. The scale is from 0-4.

The researcher	The physician	The older adult
Protocol - Usage of age limit as an exclusion criterion (23, 28, 30). - Usage of exclusion criteria which proportionally might exclude the older adults, e.g. comorbidity and PS (28, 29).	**Attitude toward the older adults** - The preconceived attitude of the patient's chronological age which prevents the invitation of the older adults to participate sufficiently in clinical trials (29, 30).	**Deprivation of autonomy** - Want to choose their own treatment and maintain their autonomy (24, 29).
Information for the older adults - Study information has not been developed for the older adults (26). - Completion of a study designed for the older adults would be extensive and time-consuming (26).	**Lack of evidence** - Lack of evidence regarding the possible toxic side effects of medicine in the older adults (29).	**Lack of understanding of the importance of clinical trials.** - Many older adults do not understand the possible benefits of participation in a clinical trial. (24, 28, 29). - The consent form used in clinical trials is too complex and detailed, which could serve as a deterrent for participation in a study (23, 24, 27, 28).
Economy - High costs associated with performing clinical trials, especially RCTs, which increases even further when older adults are included (26, 28, 30).	**Lack of resources** - Challenges of obtaining informed consent due to impaired hearing, vision, poor speech and cognitive impairment (23, 24, 26, 27, 29).	**Logistics** - Logistical challenges in particular due to financial cost of transportation and the need for extra help (23, 24, 26-29). - Lack of social network (26, 29).

Significant results and extern validity - A heterogeneous group of patients, with increased mortality and morbidity, obscures the possible effect of an intervention and increases the risk of non-significant results (23, 24). - By non-inclusion of the older adults for safety reasons compromising the chance of reaching satisfying external validity (23).	**Fear** - Fear of intoxication of the older adults while testing pharmacological interventions (23, 26, 27, 29). - Fear of non-compliance and withdrawal of the older adults before completion of the study, which impedes the possibility of significant results (26). - The inclusion of the older adults is more complicated due to comorbidities and suspicion of pharmaceutical interactions, (26, 27).	**Fear** - The older adults fear for their health if they happen to be randomized to the placebo arm of the study (24, 26, 28). - Fear of not having the optimal treatment (24).
Other - Ethical considerations: The risk of adverse outcomes must be minimal in relation to any beneficial effect when participating in the clinical studies (26).	**Other** - Lack of information about ongoing clinical trials and therefore lack of recruitment (23). - Very broad or few inclusion criteria increase the clinician's uncertainty, causing him to invite older adults to a lesser extent (19).	**Other** - Wants to retain "own" doctor and not change when participating in clinical trials (27). - The older adults do not find the outcomes of the study relevant to them (23, 29). - If relatives do not support participation, both logistically and mentally, the older adults will not participate (23, 24, 29).

Table 4 – Identified barriers for inclusion of elder people in CT according to included papers

Figure