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Review

A systematic review of trends in the selective exclusion of older participant from randomised clinical trials

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ABSTRACT

Introduction: The unjustified exclusion of older participants from clinical trials creates research populations that are non-representative, in turn creating difficulties applying research to the target populations. The aim of this study was to assess the proportion of randomised control trials (RCTs) that have unexplained upper age limits and review whether this proportion is reducing over time.

Methods: All RCTs in BMJ, Lancet, JAMA and NEJM from 1998 to 2015 were reviewed to identify any specified upper-age cut off and, if so, whether this exclusion criterion had an explanation in the text. The proportion of RCTs with an unexplained cut off was then correlated over time to look for any changes.

Results: 5680 papers were identified and 1339 excluded as they did not meet the search criteria. Of the remaining 4341 RCTs, 1258 (29%) had upper age limits specified, 1168 (92.8%) of which did not have any explanation for this cut off, a total of 26.9% of the RCTs reviewed. Over the 18-year period there was limited but statistically significant decrease in the proportion of RCTs with unexplained upper age limits (Pearson Correlation −0.609, P valve 0.007).

Conclusion: Despite being the highest consumers of medical interventions and medications, this review highlights that older patients remain under-represented in clinical trial with only modest improvements despite increasing awareness of the problem. Future research must continue to adapt to provide insight into the differential effects of medical treatments in older patients by ensuring that trial participants are representative of the patient population receiving the intended therapy.

1. Introduction

The upward trend in life expectancy means the aging population is becoming the increasing focus of clinical care (NHS Benchmarking network, 2015; National Life Tables, Office for National Statistics). As a direct result, patients over 65 years old now account for a significant proportion of medical investigations, treatments and medications taken compared to their younger counterparts, due to the age-related accumulation of chronic diseases and prophylactic prescribing based on higher absolute risk of disease (Ferrini & Ferrini, 2000). This aging population is entitled to evidence based treatments, tailored to their needs and physiology. Research developments have repeatedly demonstrated the disparate requirements and responses of this older cohort to standard medical treatments, implying that clinical trial data from younger participants cannot always be merely be extrapolated to incorporate this unique and expanding population (Mangoni & Jackson, 2004; McLean & Le Couteur, 2004).

The first study highlighting the extent of this problem throughout medical specialties was published by Bugeja et al., 1997 who found that out of 490 clinical trials reviewed, 37 (7.6%) excluded older participants for justifiable reasons, but 170 (34.7%) excluded older patients with no clear scientific explanation (Bugeja, Kumar, & Banerjee, 1997). Troublingly, this trend has been specifically observed in studies of diseases more prevalent in older age such as heart failure (Heiat, Gross, & Krumholz, 2002), cancer (Hutchins, Unger, Crowley, Coltman, & Albain, 1999; Talarico, Chen, & Pazdur, 2004; Trimble et al., 1994) and ischaemic heart disease (Gurwitz, Col, & Avorn, 1992; Lee, Alexander, Hammill, Pasquali, & Peterson, 2001) as well as in applications for ethics approval (Bayer & Tadd, 2000). As a result, generalisations regarding the treatment of older patients may be based on treatments trialled in younger, and potentially non-representative, cohorts which could be ineffective at best and harmful at worst.

Recently, there have been several attempts to assess and address why older patients are under-represented in clinical research. This includes the International Conference on Harmonisation (ICH) guidelines for industry (International Conference on Harmonisation, 1993),

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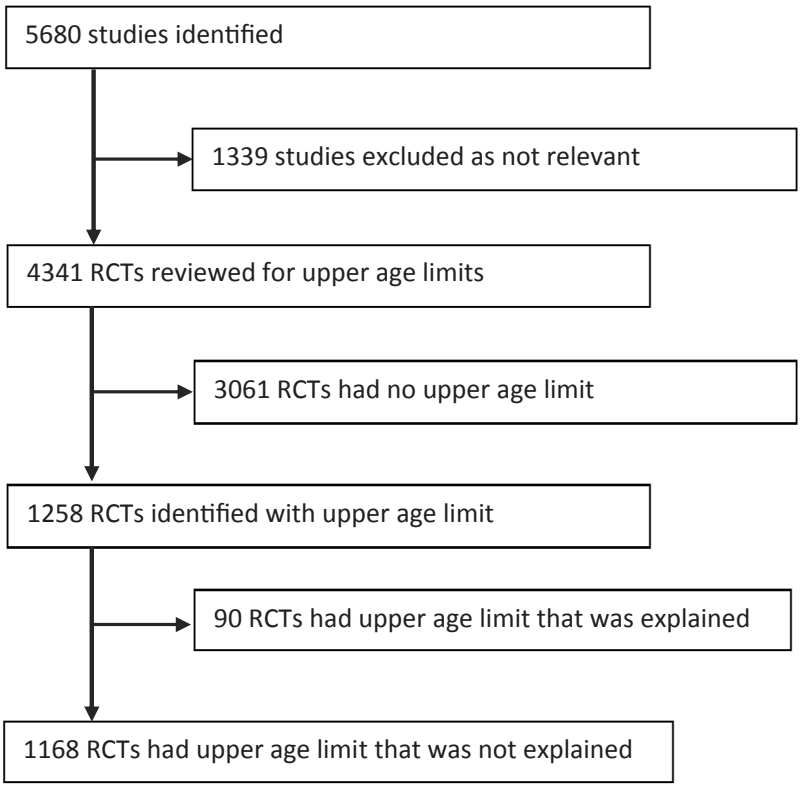

Fig. 1. Flow diagram of the systematic search process to identify RCTs for inclusion.

guidelines from the 2011 European Medicines Agency Geriatric Medicines Strategy (Cerreta, Eichler, & Rasi, 2012; EMA geriatric medicines strategy, 2011) and guidelines from the U.S. Department of Health and Human Services, Food and Drug Administration, based on ICH E7 (ICH E7, 2012). Encouragingly, a PREDICT consortium has been established to assess why older patients are under-represented in clinical research and propose ways to boost their inclusion (Bartlam et al., 2010; PREDICT 2020 Horizon, 2007). PREDICT have suggested numerous practical changes to commissioning, recruitment and conduct of clinical trials. This includes easier physical access to research institutions, limited exclusion criteria, simplified protocols and consent process, more emphasis to the patient about the benefits of trial participation, home visits, financial rewards for inclusion and more detailed training for research staff. PREDICT have also outlined a Charter to provide a framework to protect the rights and privileges of older people in clinical trials. This is similar to the Infants, Children and Young People's Charter for Child Health Research designed to address the paucity of infants in clinical trials (Infants & Young Children Charter, 2016) due to the lack of legal capacity to consent and concerns over their welfare.

Despite increasing public and regulatory awareness of this issue, there has not been a recent attempt to quantify the extent of age-related bias in publications across all specialities and assess whether this has changed over recent years. We therefore designed a review to analyse whether the situation is changing by assessing the trends in published RCTs with unexplained upper age limits.

2. Methods

2.1. Systematic review

A systematic search was performed for English language original human randomised controlled trials in New England Journal of Medicine (NEJM), British Medical Journal (BMJ), Lancet, and Journal of the American Medical Association (JAMA) from January 1st 1996 to December 31st 2015. This search was performed via Pubmed in April 2016 using the search terms 'randomised control trials' or 'RCT', searching all fields including title and methods. This allowed for inclusion of all types of RCTs; pharmacological, behavioural and clinical. These four journals were selected as they were the top non-specialty specific journals by impact factor (Annals of Internal Medicine was excluded due to the small numbers of RCTs published per year). Randomised control trials were selected as they are generally considered to provide the most robust evidence for clinical practice and therefore the study populations should be designed to be representative of the target population.

2.2. Data collection

The identified articles were reviewed by title and abstract to exclude any commentary articles, duplicates, reports that were not RCTs or any trials not related to the adult population such as studies related to child or adolescent health or studies related to practitioner behaviour with no patient recruitment. Any publications where we were not able to access the full text were excluded and we excluded any entire years where we were not able to access > 90% of the RCTs. No other exclusion criteria were applied.

The remaining manuscripts were then formally reviewed by two reviewers to assess for an explicit upper age limit. This information was usually found in the abstract or methods section but occasionally was found elsewhere in the text or referenced in other papers (e.g. previous publications by the same authors). For any paper that had an upper age limit, the text was then searched to see if there was an explanation for this, making no judgement as to whether this explanation was valid or appropriate, and we included a subsection for papers specifically relating to older people, defined as any RCTs with a lower age limit above 65 years old.

2.3. Data analysis

The number of trials with explained and unexplained age limits were calculated as a proportion of the total number of RCTs included in the review. The correlation coefficient r of RCTs with unexplained