Ageism And Clinical Research

Abstract:

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Abstract
Despite being the most significant consumers of health care resources and medications worldwide, recent international research has highlighted the under-representation of older participants from clinical trials. This creates problems for physicians as the patients seen in clinical practice are not representative of those on which medical treatments and interventions have been trialled, and we need to consider whether results (both negative and positive) from these trials are applicable to these patients. Our aim was to gauge whether exclusion of older people was prevalent in research proposals submitted to Dublin teaching hospitals. We audited all clinical research proposals submitted to the Research Ethics committee (REC) covering the teaching hospitals attached to Trinity College Dublin (TCD) from July 2008 to July 2011 inclusive, recording exclusion of patients based on an arbitrary upper age limit. Of the 226 relevant trials studied, 31 (13.7%) excluded participants based solely on an arbitrary upper age limit. 22 (9.8%) of the relevant trials were submitted by geriatricians, none of which excluded patients based solely on age. Over 50% (12 of 22) trials submitted by neurology/psychiatry excluded patients based on an upper age limit. The mean upper age limit used over all trials as a cut-off was 69.2 years of age. As well as this, the majority of the remaining trials also contained other exclusion criteria, especially those based on cognitive function which further limited participation of older people.

While we found that a significant proportion of clinical trials submitted to the TCD REC still excluded patients based arbitrarily on an upper age limit, participation rates of older people seem to be higher in this Irish centre than that seen in international trials. Significant room for improvement still remains however and there needs to be a promotion of greater awareness of the need for developing, testing and licensing medicines so that it mirrors the consumer groups in which they will be used. Increased input from geriatricians around the testing and licensing of medicines, and in licensing agencies, would greatly help in this regard. It is both unhelpful for optimal healthcare as well as fundamentally unjust to exclude participants from clinical research based solely on an arbitrary age limit.

Introduction
One of the paradoxes of modern medicine is that while it is widely recognized that older people are proportionately the most significant demographic group of consumers of health care [1], including medications [2], they are in general poorly represented or even absent in clinical trials relating to the licensing of medicines [3]. This mismatch between the needs of a large group of patients and the lack of due inclusivity in the research base for evaluating new therapies is a cause for major concern to geriatricians and gerontologists, with a recent position paper from the European Union Geriatric Medicine Society and the American Geriatrics Society [4]. There are also concerns about the exclusion of older participants with frailty, a further challenge as frail older people also consume considerable amounts of medications. Recent international research has highlighted the extent of the exclusion of older patients from clinical trials. Cherubini et al found that 26% of trials investigating treatments for heart failure excluded patients based on an arbitrary upper age limit [5], while Bugeja et al found that up to a third of all original research papers in major medical journals excluded elderly people without justification [3].

This obviously creates problems for physicians as the patients involved in trials are not representative of those seen from day to day in clinical practice: for those who are aware of the disparity, they are uncertain whether positive (and indeed negative) results obtained in trials of younger patients can be applied to older patients. Those who are unaware may be unknowingly prescribing medications in good faith without the assurance of an evidence of efficacy and harm. In addition, under-representation in clinical research may disadvantage older patients in that they may denied specific, potentially efficacious, treatment, as there is no relevant evidence base on which to base clinical decision making in this age group. An example is thrombolysis for ischaemic stroke where the licensed indication is for patients up to 80 years of age [6]. An assessment of clinical research in Ireland and the inclusivity of older participants has not yet been carried out. Our aim was to gauge whether such practices were prevalent in research proposals submitted to Dublin teaching hospitals.

Methods
We audited all clinical research proposals submitted to the Research Ethics committee (REC) covering the teaching hospitals attached to Trinity College Dublin (TCD) over a 3 year period from July 2008 to July 2011 inclusive. We excluded non-clinical studies and those in which inclusion of older participants would not be expected, e.g. fertility studies. We then examined the inclusion and exclusion criteria for each proposal, and recorded exclusion of patients based on an arbitrary upper age limit and whether this was justified or unjustified. We also noted any exclusion criteria, for example those based on cognitive function or polypharmacy, which would also limit participation of older patients.

Results
In total we examined 278 clinical trials, 226 of which were determined to be relevant to our study: 22 (9.8%) relevant trials were submitted by geriatricians, none of which excluded participation on the basis of age. Of these 226, 31 trials (13.7%) excluded participants based solely on an arbitrary upper age limit. The mean upper age limit used in these trials was 69.2 years of age. The upper age limit was most notable in studies submitted by physicians specialising in neurology and psychiatry (12 of 22 studies, 55%) followed by oncology (5 of 21 studies, 23%). Almost 39% (12 of 31 trials) of research excluding participants based on an arbitrary upper age limit was submitted by physicians specialising in neurology /psychiatry, over 22% (7 of 31 trials) came from gastroenterologists, while over 16% (5 of 31 trials) were haematology

/oncology trials. Despite Cherubiniâ s findings, only 7.14% of the trials submitted by physicians in cardiology excluded patients based solely on age. As well as this, a significant proportion of the remaining trials contained further exclusion criteria, especially those based on cognitive function, which would limit the participation of older adults: in general this was left at the clinical discretion of the researcher, and in only one case was a lower limit of the Mini-mental State Examination [7] specified.

Discussion

Our results show that, while a significant minority of clinical trials still exclude patients based arbitrarily on an upper age limit, participation rates of older people seem to be higher in this Irish centre than those seen in international trials. However, this does not justify complacency, given the likely increase in our ageing population and the need to ensure that medications are appropriately tailored to the needs of this population. A first step would be the development of a greater awareness among physicians, regulatory authorities and the pharmaceutical industry of the need to change the testing, evaluation and licensing of drugs to more accurately mirror the needs of key consumer groups, particularly the frail older person. It is encouraging that a major European project has focussed on increasing involvement of older patients in clinical research [8], and this has helped raise awareness of the issue. In addition, the development of trials such as IST-3, specifically designed to investigate the safety and efficacy for thrombolysis for ischaemic stroke in those over 80 years of age demonstrates an increasing awareness among physicians of the need to age-attune the evaluation of medicines to those most likely to both need and consume them [9].

In turn, expertise in geriatric medicine is lacking in many national medicines licencing agencies in Europe, with 90% having neither committees nor policies relating to prescribing to older people. However, it is encouraging that over 67% acknowledge that geriatric medicine input would be beneficial [10]. In addition, the European agency for licensing medicines, the European Medicines Agency, has responded to advocacy from geriatricians to develop a strategy for developing a more age-attuned system, even if this falls short as yet of the status and formal engagement of its Paediatric Committee at the other extreme of life [4].

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Comments: