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Clinical trials in older people: are we being ageist?

Peter Crome*

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The next few decades will witness a large increase in the number of older people in the population, principally those aged 80 and over. This age group also has the highest prevalence of disease and disability. Therefore, one might expect that the evidence base on how best to treat this group would be well established, but this is not the case. Older people, especially those with physical and mental health comorbidities, continue to be unjustifiably excluded from clinical trials [1,2]. This raises the question as to whether the exclusion of older people from such investigations can be considered as ageist and whether, as a consequence, older people suffer from age discrimination.

What do we mean by ageism?

The introduction of the word ageism, which is generally attributed to the US gerontologist Robert Butler, is relatively recent. The Oxford English Dictionary defines it as "prejudice and discrimination on the grounds of an age of a person." It is usually considered alongside other 'isms' such as sexism and racism, although its incorporation into equalities legislation, at least in the UK, is more recent, for example compulsory retirement on the grounds of age was only outlawed in 2011. Ageism has, as its basis, an irrational belief that there is an inevitable decline in physical and mental abilities in old age, and that in turn makes older people less worthy to receive societal benefits. At first sight this may seem far away from the world of clinical trials. Those involved in clinical trials would probably be aghast at being labeled as ageist, either in regard to the design of clinical trials or in the implication that they have an underlying prejudice against older people. It can be direct or indirect and subtle. Direct age discrimination includes fixing arbitrary age limits for certain procedures or, in the context of this article, entry into clinical trials. This may be justified for diseases or conditions that do not occur in later life (such as pregnancy) but usually it is not. As with other 'isms', indirect discrimination can be more subtle. Probably the most important cause of indirect discrimination is the unnecessary exclusion of people with comorbidity, disability and those who take multiple medications. It also includes not taking into account any special needs that older people might have. For example, they are more likely to have hearing or eyesight problems, so that patient information (including those related to clinical trials) may need to be modified. Similarly, basing clinical trials in centers to which older people are less likely to be referred, amounts to indirect discrimination. Thus, indirect discrimination often results from ignorance or failure to consider older people specifically, rather than malign intent.

Ageism & human rights

When considering ageism and age discrimination, it is now necessary to place

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*Department of Primary Care & Population Health, UCL (Royal Free Campus), Rowland Hill Street, London, NW3 2PF, UK
Tel.: +44 (0)20 7830 2239
E-mail: p.crome@ucl.ac.uk

it not only in a general moral and ethical framework, but also within the concept of

Human Rights legislation. The right to life, the prohibition of degrading treatment and the right to privacy all have relevance within the concept of clinical trials. Given that the research ethics framework arose in the wake of Nazi medical experimentation and other trials where consent was not obtained, it is not surprising that for a long time the need to avoid exploitation of vulnerable groups has predominated. More recently, this approach has been balanced by a greater emphasis on autonomy, which includes the right of older people to make their own decisions. Indeed this aspect has been incorporated into government policy with the development of National Institute for Health Research networks. Within the healthcare system, ageism most obviously manifests as humiliating or patronizing care, or denial of access to certain treatments and services. This has been described in numerous reports such as the recent National Audit of Dementia [101].

The impact of ageism

A good starting point when considering whether clinical trials are ageist or not is to consider practitioner–patient decision making when undertaking diagnostic and screening procedures or treatments. If an older person is at a disadvantage when compared with a younger person, because of a lack of evidence of efficacy, potential risks or both, then age discrimination has occurred. Extrapolation from the results in younger people is always going to be second best [3].

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Much of the emphasis in the literature on older people and clinical trials has been on their under representation. This continues to be a major problem, but the issue is broader. Lack of funding for basic research into conditions such as dementia and frailty means that major diseases of later life will not be studied. Similar considerations apply to health services research where the impact of the demographic shift on the overall function of the health service has yet to be translated into major research activity. If regulatory bodies require only minimal evidence of effects and side effects in older people before licensing, then it is not surprising that new treatments become generally available before it is possible to give accurate advice for older people. Such advice may be a long time coming. The confirmation that treating hypertension in the over 80s has a role is being reported half a century after modern drugs were first introduced [4]. The use of new treatments is governed by regulatory bodies and clinical guideline services, such as those produced by NICE in the UK. NICE's recommendation on alteplase in stroke patients is that "It should only be administered in centers with facilities that enable it to be used in full accordance with its marketing authorization" [102]. Since the drug's use in those aged over 80 years is not authorized by the licensing authority, older people are less likely to be treated. The rational for this decision is based on a lack of trial evidence. This disadvantage, for a condition with a median age in hospital of almost 80 years [103], is likely to be compounded by delays in diagnosis and referral to treatment centers with the appropriate facilities.

Evidence from the PREDICT study

The findings of the PREDICT study have provided up to date evidence of the extent of age discrimination and the views of professionals and patients on this subject. In a systematic review, Beswick *et al.* identified a number of barriers to and promoters of inclusion of older people into clinical trials across a wide range of conditions, including Alzheimer's Disease, heart failure and colorectal cancer, all of which typically studied patients 10 years younger than the median age of people with the disease [5]. Identified barriers to recruitment included absence of requirement to study older people and concerns about the impact on patients and practice. Patients were worried about any detrimental effect on care and treatment risks, together with practical issues such as transport, the costs of taking part, time involvement, impact on caring and the quality of received information. However, very few controlled trials had satisfactorily investigated the impact of any interventions to improve recruitment. In a complementary study, Cherubini *et al.* concluded that 25.9% of current cardiovascular trials recorded on the WHO clinical trials platform had an unjustifiable upper age limit with an overall exclusion rate of 43.4% when such factors as medication, comorbidity and disability were also considered [1]. Interestingly, they also found that unjustifiable exclusion was twice as likely in the EU compared with the USA (32.3 vs 16.2%; $p = 0.007$). Drug trials sponsored by pharmaceutical companies were also far less likely to have poorly justified exclusion criteria than those sponsored by public bodies (13.9 vs 35.6%). This suggests that trials conducted for regulatory purposes are now being planned with more thought applied to unnecessary exclusion criteria by the sponsors or by the requirements of the regulatory authorities. Perhaps this indicates a degree of progress. In an independent study of ethics committee

submissions to a Spanish center, Cruz-Jentoft and Gutierrez also showed a progressive reduction in arbitrary age limits [6]. Having established that age exclusion continues to be an issue, the PREDICT project examined the views of over 500 professionals (GPs, nurses, geriatricians, clinical trialists, ethicists and industry pharmacologists) on the impact of these findings. Not surprisingly, geriatricians were the most concerned about this under-representation and overall 79 and 73% of respondents believed that practitioners and older people were disadvantaged by this, respectively. Less than a fifth of respondents thought it was justified to exclude people from trials on age grounds alone, but a half thought that exclusion because of polypharmacy and comorbidity were justifiable exclusion grounds. Additionally, even if specific age limits were removed from trial protocols, it was believed that trialists would still be reluctant to recruit older people because of comorbidity and disability. Respondents from Eastern Europe were less likely to be dissatisfied with the present situation and were less in favor of regulatory changes. This is likely to reflect their recent political history, with practitioners preferring the greater availability of treatments for older patients over their more thorough evaluation [7]. Ageism was one of the themes to emerge from a series of focus groups held across the participating countries. To quote from one dementia carer, "in my opinion, they're discriminating against older people in clinical trials and that where it's appropriate they should be included," and from a stroke group in Italy, "medical research is for everybody." It was recognized that older people might respond to drugs differently: "I cannot believe it! The drugs usually prescribed to older persons have been only tested in adults or young people! How is it possible that doctors prescribe them to older people?" Other themes to emerge were the importance of trust and the need to support participation.

Conclusion: the way forward

Apologists for the status quo will cite fears of missing the 'effect signal' amongst a sea of comorbidity, high adverse event and drop-out rates, increased costs and time to study conclusion and lack of interest amongst older people as justification for low inclusion. These may be true if trials are planned without taking into account the real world for older people. They should be seen as issues to be taken account of, rather than as barriers [8]. Indeed, the rates of people refusing to enroll in trials or failing to meet inclusion criteria are often in their teens or fewer [9]. Given the vast differences that exist between different types of clinical trials and Governments' and researchers' desires to see a reduction in regulation in this area, it is not possible to suggest a one size fits all set of recommendations. However, the PREDICT Charter provides a sensible framework for planning for the future, taking into account key principles of safety and autonomy [104]. Essentially, the Charter requires all those involved in clinical trials: the sponsors, the regulatory and ethics review bodies and the practitioners conducting the study, to think 'older person.' The Charter incorporates the principles of human rights, including the demand that older people should be offered evidence-based treatments and should not be discriminated against in trial recruitment. With the involvement of older people, trial design may have to be modified so that there are more intensive regimes for younger, fitter people but less strenuous demands for older people and those with comorbidity [10]. There is always a need to ensure user involvement is not tokenistic. Older people put more emphasis on quality of life rather than increased life expectancy, and outcome measures may need to be adjusted. Telephone follow-up should be used whenever possible. A redefinition of older as over 75 rather than over 65 years of age by regulatory bodies should also help [105]. The key is to consider the needs of older people and their inclusion in trials from the outset of an overall project and not just as an add-on after thought, or worst of all, not to think about them at all.

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