Inclusion of older people in interventional clinical trials

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The population growth and demographic changes have been remarkable in the past century, leading to a massive growth in the older population. Older people constitute the largest group of consumers of medications globally and will continue to be so for the foreseeable future. There has been chronic and unjustifiable underrepresentation of older people in interventional clinical trials, as has been evident in the majority of landmark studies that have been designed to address questions very pertinent to older people as well in many different medical specialties. Chronological age itself or comorbidity, or both in combination, have been instrumental directly or indirectly for systematic exclusion of older people from these clinical trials. Hence the evidence base for treating older people with medical conditions that usually tend to coexist in a given older person is rather patchy and dubious, leading to speculation of benefit from interventions as a result of extrapolation of inferences from trials in younger populations and also placing older people at risk of harm from dreadful adverse effects of medications of which the benefits for them are unproven. There are many expressed and unexpressed reasons for existence of direct and indirect age discrimination in interventional clinical trials. Researchers and pharmaceutical companies along with inertia of research ethic committees and professional bodies, which play a role of advocacy for older people, will have to share the blame and responsibility for the current state of deplorable affairs pertinent to medical research in older people. Answers to the lack of enthusiasm for including older people in clinical trials would be many, but will definitely involve changes in the attitudes of researchers. It will also require enforcement of legislations for proportional representation of older people in clinical trials in keeping with incidence and prevalence of diseases amongst them.

Keywords: clinical trials • elderly • exclusion • inclusion • medical research • older people• participation • underrepresentation

Population trends & epidemiology of diseases

Over the past century the world has witnessed revolutionary changes in population growth and changing demographic trends. The global life expectancy at birth has risen from 56.4 to 67.5 years for men and from 61.2 to 73.3 years for women from 1970 to 2010 [1]. In Western Europe the average life expectancy at birth has risen from 68.5 to 77.9 years and 74.7 to 83.2 years during the same period for men and women, respectively [1]. The health of the population of the world has been in a transition and as a result, it is expected that the number of people aged 60 years and over will continue to grow at the fastest pace ever with an expected rise of more than 50% over the next four decades, rising from 274 million in 2011 to 418 million in 2050 [2].

Population ageing is predicted to continue with the number of people over the newly legislated pension age increasing by 28% from 12.2 to 15.6 million by 2035

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in the UK [201]. By then, the percentage of people over the age of 65 years in the UK will account for 23% of the population [202]. The greatest rise in population is projected to be for the oldest of the older age group. By 2035 it is projected that the number of people aged 85 and over will be almost 2.5-times larger than in 2010, reaching 3.5 million and accounting for 5% of the total UK population [202]. The projected increase in the number of older people in conjunction with reducing fertility rates means that the average age of the UK population will also continue to rise.

Increased longevity of mankind unfortunately comes at a price of heavy disease burden of noncommunicable diseases, which are more prevalent in older population. The years added to life also come along with diminishing physiological reserve and failing homeostasis or frailty in older people. In 2010, the number of people living with dementia has been estimated to be 35.6 million worldwide [3]. The numbers are expected to almost double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050 [3]. Approximately 1% of the population over 60 year of age has Parkinson's disease [4]. In one review on population-based studies, the age-standardized prevalence of stroke for people aged 65 years or more has ranged from 46.1 to 73.3 per 1000 population, but has ranged from 58.8 to 92.6 per 1000 population for men, and from 32.2 to 61.2 per 1000 population for women [5]. The number of hip fractures occurring in the older population of the world has been projected to rise from 1.66 to 6.26 million from 1999 to 2050 [6]. The number of diabetics over the age of 64 years in the developing countries has been estimated to be more than 82 million, while those in the developed countries has been predicted to be more than 48 million [7]. In Framingham cohort, the prevalence of definite hypertension in the older men and women has been found to be 40 and 50%, respectively [8]. Given that the current world population exceeds 7 billion and those who are aged 60 and over exceeds 274 million [2], the magnitude of the disease burden is not difficult to comprehend.

Existence of comorbidity is common among older people. Prevalence of multimorbidity increases in all age groups from 10% in under 20 years of age up to 78% in those who are aged 80 and over [9]. In a systematic review undertaken on studies published in Australia between 1996 and 2007, 80% of the older population was found to have three or more chronic conditions [10]. In that review, over 50% of those who had arthritis were also found to have hypertension, while 20% had cerebrovascular disease, 14% had diabetes and 12% had mental health problems. Over 60% of patients with asthma had reported arthritis as a comorbidity, 20% also had cerebrovascular disease and 16% had diabetes. Of those suffering from cerebrovascular disease, 60% also had arthritis, 20% diabetes and 10% had asthma or mental health problems. What this also translates into is that use of medications is likely to be several folds higher in older people compared with the younger generations. Studies have demonstrated that medication use increases with age and many people over the age of 65 use at least three prescription medications in developed countries [11,12].

A case for involving older people in interventional medical research

Given the prevalence of chronic disease, the trajectory of population growth along with demographic changes and the existence of multimorbidity in the older age, it is not difficult to fathom that the older population is likely to represent the largest and still-growing sector of consumers in the pharmaceutical market. Therefore, it is logical to expect that there should be adequate representation of older people in interventional clinical research, that the researchers have a duty to involve older people in research related to conditions that affect older people and that older people themselves have a right to be involved in medical research.

Adverse effects of medications are common in older people. The overall rate of adverse drug reactions in a study of older people living in the community taking medications was found to be 50 per 1000 patient-years, which is equivalent to a number needed-to-harm of 20 [13]. Many current clinical practice guidelines, with a few exceptions, are meant to be adopted universally across all ages of adult population and are based on hitherto available evidence. Such generalized guidance is likely to be unscientific, misleading and perhaps harmful as they tend to generalize management standards by extrapolating evidence to capture those sectors of the population that were not represented, or underrepresented, in clinical trials upon which the guidelines are founded. Many medications used in chronic medical conditions do tend to have adverse effects and therefore it is ethically unacceptable and unjustifiable to use these medications if the safety is not properly tested in older people in clinical trials, even though many guidelines such as chronic heart failure management guidelines issued by both NICE and American College of Cardiology/American Heart Association and NICE diabetic neuropathic pain management guidelines stipulate their use universally across all ages of adults [14-16]. Presence of comorbidity may negate the benefit rendered by a medication in one clinical condition by posing a greater risk or a disadvantage in another coexisting medical condition. Many practitioners may vouch for the fact that a

combination of trial-proven medications including β blockers, aldosterone antagonists, angiotensin converting enzyme inhibitors and angiotensin receptor blockers given in systolic dysfunction of the heart could cause significant postural hypotension and subsequent falls that may lead to hip fractures in frail older people. In fact, the association between medication use and risk of falls have been well established [17–19]. Therefore, anticipation of benefit of mediations by extrapolation of evidence may not be ideal for the health of older people.

Many widely available current clinical guidelines are designed to give management guidance of specific medical conditions taken in isolation [203]. To date, only a few guidelines such as the Joint National Committee 7th report and the Annual Diabetes Guidelines published by the American Diabetic Association have taken comorbidity into account in their given guidance, irrespective of the fact the comorbidity is a common phenomenon in older people or the largest users of the healthcare resources of the day and age [20,21]. This is probably a reflection of lack of pragmatic research data in older people with comorbidities.

Cost of healthcare has now drawn attention of many nations without the exception of the wealthiest nations in the developed world, including the USA and many of the nations in Western Europe [22,23]. Sustainable healthcare may not be feasible unless ever increasing costs are brought under control. However, duty of care to patients overrides the cost implications in principle. In practical terms, this means the treatment has to be justified on the grounds of proven benefit, meaning that funding will not be available for therapies that are not proven in clinical trials, forcing the clinician to practice evidence-based medicine. Practicing evidencebased medicine is difficult when the evidence available is limited and not robust. Hitherto available evidence in many areas of medicine, with regard to older people and the oldest of the older people in particular, cannot be the highest quality as the number of trials in them are limited and the number of older people involved in the clinical trials is also limited. This makes the evidence obtained, even through processes such as post hoc subgroup analysis, not very reliable. Therefore, it is likely that older people will suffer due to speculation of either benefit of or lack of proven efficacy of treatment. The lack of evidence of benefit due to dearth of data does not equate to evidence of lack of benefit of a given medical intervention. Denial of therapy to older people on the assumption of lack of benefit amounts to age discrimination [24]. For these reasons older people should be, or should have been, adequately represented in clinical trials designed for assessment of therapeutic interventions.

Involvement of older people in interventional clinical trials; the current state of affairs

There is ample evidence that demonstrates exclusion of older people without justification from interventional clinical trials. A systematic review published in 2001 of 593 randomized control trials on acute coronary syndrome found that there had been an explicit age cut-off for enrolment in 40% of them [25]. Although the trial enrollment of patients aged 75 years or older had increased from 2% for studies published during 1966-1990 to 9% during 1991-2000, this had been found to be a gross underrepresentation of patients with myocardial infarction (which was 37%) in the USA [25]. A more recent systematic review that included 357 articles undertaken by the PREDICT study group revealed that treatments for common conditions, such as heart failure, hypertension, Alzheimer's disease, depression and colorectal cancer are evaluated inadequately in older people [26].

Logically, representation of the participants in a clinical trial should mirror the burden and dispersion of disease within the population based on the incidence and prevalence of disease within different age strata rather than be proportional to the 'head count' in a given age cohort. Currently there is a great mismatch between the numbers of older people represented in clinical trials and the actual disease burden they carry as a cohort of the population, as the prevalence of disease is much higher with advancing age.

Landmark clinical trials & underrepresentation of older people

Landmark trials are those trials that are of substantive influence on the clinical practice of medicine either by appealing to the minds of individual practitioners or by contributing to formation of clinical management guidelines with regard to a given clinical condition. Analysis of baseline characteristics of participants along with the inclusion and exclusion criteria for enrolment in large multicenter landmark clinical trials that have had a major impact on the current medical practice and have been heavily sponsored by pharmaceutical industry, may show the situation for older people in major clinical trials. The research subjects are often healthier and younger than the average patients who need the intervention most. The trials that will be laid out in the next few paragraphs are only exemplary and by no means exhaustive.

Trials in cardiovascular diseases

The Rotterdam Study, which was a prospective population-based cohort study in 7983 participants aged 55 or over, showed the prevalence of heart failure was higher in men and increased with age from 0.9% in subjects aged 55-64 to 17.4% in those aged 85 or over [27]. However, the landmark trials that assessed interventions for heart failure do not reflect this reality. The SOLVD study was a randomized, double-blind, placebo-controlled, multicenter trial that evaluated the effects of enalapril on survival in heart failure [28]. The mean age of the participants of SOLVD was 62 years with an upper age limit of 80 years for enrolment. The study also excluded people with 'life-threatening' diseases. The VHeFT-II study compared the effect of enalapril against the combined effect of hydralazine and isosorbidedinitrate in congestive cardiac failure. The mean age of the participants in this study was only 60.5 years [29]. The investigators of this study imposed an age cut-off of 75 years and excluded those who had a 'limited life expectancy' [29]. In the DIG trial, where effects of digoxin on mortality from any cause in patients with heart failure in sinus rhythm were studied, the average age of the trial participants was 63.5 years with a SD of \pm 11 years [30]. The investigators reported that nearly 27% of the participants were over the age of 70 years in this study. According to the principles of Gaussian distribution, mean ± 1 SD includes 68.3% and mean ± 2 SD include 95.4% of the population [31]. Therefore, the logical inference would be that participants over the age of 80 and 85 years would have been minimally reprtesented, perhaps less than 10% and certainly less than 2.5%, respectively; over these age demarcations, representing the upper tail end of the study cohort in the DIG trial. The HOPE study, which assessed the effects of an angiotensin converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients, demonstrated that ramipril significantly reduced the rate of death, myocardial infarction, and stroke in a broad range of high-risk patients who were not known to have a low ejection fraction or heart failure. The mean age of those who took part in this study was also 66 (SD ± 7) years [32]. The CIBISS-II trial, which was the first large study to demonstrate the beneficial effects of β blockers (bisoprolol) in heart failure, had an exclusive age cut-off of 80 years with a mean age of its subjects of 61 years [33]. The mean age of the study recruits of the MERIT-HF trial, which studied the effects of metoprolol extended release in advanced heart failure and the RALES study, which evaluated the effects of aldosterone on severe systolic dysfunction of the heart was $63.9 \text{ (SD } \pm 9.5)$ years and 65 (SD \pm 12) years, respectively [34,35]. The latter study also excluded people with 'life threatening diseases' and no break-down of the comorbidities of those who were involved in the study was published with the results. The mean age of the participants of the ATLAS study, which compared the effects of low dose of lisinopril against high dose on morbidity and mortality in heart

failure, was not different to other studies and it was 63.6 $(SD \pm 10.3)$ years [36]. A study that assessed the effects of valsartan on mortality and morbidity plus mortality (Val-HeFT trial) and a study that evaluated the effects of carvedilol on survival in patients with severe heart failure, had recruits of a mean age of 62.4 (SD ± 11.1) years and 63.5 (SD ± 11.5) years, respectively [37,38]. The average age of the subjects of the COMET study, which assessed the effects of carvedilol against metoprolol on chronic heart failure, was 62.4 years with a SD about the mean of 11.3 years [39]. The interquartile range of the participants of SCD-HeFT, which evaluated the effects of implantable cardiac defibrillators on sudden death compared against amiodarone, was 51.7-68.3 years with a median age of 60 years [40]. Therefore, it appears that all these studies that provided the evidence base in treating heart failure in current medical practice had excluded the oldest of the old, in whom heart failure is more prevalent, as only 2.5% of the participants in these studies were above the age of 85 years at maximum. The series of CHARM studies were notable in excluding females, especially those who were older than 75 years of age [41-45]. In these studies only approximately 18-23% of the study subjects were over the age of 75 and approximately 75% of the samples consisted of males [41-45]. The SENIORS trial, which was designed to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure, was confined to those who were over the age of 70 years. Baseline characteristics of the patients in this trial appeared to represent a healthier cohort of older adults and the mean age of the participants was 76 years with a SD of 4.7 years, implying that still only a maximum of 2.5% of the study population was perhaps older than 85 years [46].

The incidence and prevalence of acute myocardial infarction increase progressively with age. In the USA, over 60% of acute myocardial infarctions occur in patients 65 years of age or older, and approximately a third occurs in persons over the age of 75 [47]. Nevertheless, large thrombolytic trials such as GUSTO trial, which compared the effects of four thrombolytic strategies on mortality, namely streptokinase with subcutaneous heparin, streptokinase with intravenous heparin, accelerated t-PA with intravenous heparin and streptokinase with t-PA and intravenous heparin, included much younger patients with a mean age of 62 years [48]. A subsequent study assessed medium to long-term outcome of patients who were ineligible for thrombolysis and hence, received no thrombolysis or nontrial thrombolysis compared with those enrolled in a clinical trial of thrombolysis, including previously mentioned GUSTO trial [48]. It was then found that patients enrolled into thrombolytic trials were at low-risk and

those who were deemed ineligible for thrombolysis were at high-risk, received less surveillance, were less likely to be revascularised or receive trial-proven treatments, and had a poor long-term outcome [49]. Patients recruited into thrombolysis trials were significantly younger by almost 10 years than those deemed ineligible for thrombolysis in these trials [49]. A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital thrombolysis in acute myocardial infarction patients gathered individual patient data from 22 trials [50]. It demonstrated that primary coronary intervention was associated with a significant 37% reduction in 30-day mortality. However, the median age of the pooled recruits was about 63 years with an interquartile range of 52–74 years [50]. Similarly, in large multicenter randomized clinical trials that evaluated the benefit of statin therapy following myocardial infarction, older people have been underrepresented. In the IDEAL trial, which compared the benefit of atorvastatin against simvastatin, the average age of the subjects was 62 (SD \pm 9.5) years [51].

Hypertension is prevalent in older people. Many randomized clinical trials have been conducted with regard to treatment of hypertension in the population. The MRC trial of hypertension in older adults was launched to establish whether treatment with β blockers reduces strokes, coronary heart disease and death in older adults [52]. However, the study was confined to those who were aged between 65 and 74 years with a mean age of 70 years. The SYST-EUR trial, which assessed the impact of active treatment of isolated systolic hypertension on cardiovascular complications did not have any age restrictions [53]. However, in spite of the prevalence of isolated systolic hypertension of >25% in those over the age of 80 years compared with 8% of those over the age of over 70 years, the mean age of the recruits in this study was 70.25 years [53]. The ABCD trial, which demonstrated significant benefit of enalapril therapy over nisoldipine in patients with diabetes and hypertension, was confined to those who were less than 74 years with a mean age of participants of 57.2 years [54]. Effects of intensive blood pressure lowering and low-dose aspirin were studied in patients with hypertension in the HOT trial where the total size of the sample was 18,790 and this study enrolled only those who were between 50 and 80 years of age, with a mean age of 61 years of its recruits [55]. The STOP-2 trial enrolled 6614 patients aged 70-84 years with a mean age of 76 years and demonstrated that there was no significant difference between what was then regarded as conventional antihypertensives and what was then recent on the market as newer antihypertensives, in terms of reducing cardiovascular morbidity and mortality [56]. However, the oldest of the older

people have been excluded from this trial in spite of its intensions. The INDANA group published a subgroup meta-analysis of pooled data of seven large clinical trials in treatment of hypertension in older people in 1999, and recognized that treatment of hypertension has not been adequately studied to ascertain the benefit of treatment in people over the age of 80 years of age [57]. There were only 1670 patients over the age of 80 years included in these seven studies, which had a pooled total of 15,587 participants who were 60 years or over, representing 11% of the total cohort [53,57-63]. The mean age of 6105 participants in the PROGRESS trial, which studied the efficacy and safety of blood pressure lowering in both hypertensive and nonhypertensive patients with cerebrovascular disease was 64 years, although there was no explicit age limit for the enrolment of the trial [64]. The LIFE trial evaluated the effects of losartan in reducing the cardiovascular mortality and morbidity against those of atenolol by enrolling 9193 patients, of whom the average age was 66.9 (SD \pm 7) years and excluded patients above the age of 80 years from the trial [65]. The aim of the ALLHAT trial was to determine whether a calcium channel blocker or angiotensin converting enzyme inhibitor lowers the incidence of coronary heart disease or other cardiovascular diseases compared with treatment with a diuretic, and it established that diuretics are better as the first-line therapy but the average age of patients in this study was only 66.7 years despite the fact that there were 33,357 patients enrolled in the study [66]. The average age of the patients was 67.3 $(SD \pm 8.1)$ years in the VALUE trial, which established that both valsartan and amlodipine lead to equal outcomes when used to treat hypertensive patients at high cardiovascular risk by enrolling 15,245 patients [67]. The ASCOT-BPLA aimed to compare the effects of a combination of atenolol with a thiazide diuretic versus amlodipine and perindopril on nonfatal myocardial infarction and fatal coronary heart diseases, for a given reduction in blood pressure, by enrolling 19,257 hypertensive patients [68]. However, the investigators excluded patients over the age of 79 years from this trial [68]. There were no specific age cut-offs set in the ONTARGET trial, which compared ramipril, telmisartan and a combination of both in high-risk diabetics or patients with vascular disease without heart failure and enrolled 25,620 patients [69]. However, inclusion and exclusion criteria published with the supplementary information of this study reveals that patients who had a history of syncope, uncontrolled blood pressure defined as that over 160/100 mmHg, other major noncardiac illness or illness expected to reduce life expectancy were excluded. These exclusion criteria were very likely to have indirectly discriminated against older people and have them excluded from the trial as these are common conditions and situations among older people. Similarly, the ACCOMPLISH trial, which demonstrated benazepril plus amlodipine combination was better than benazepril plus hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension, excluded patients with concomitant illness or mental health conditions that could interfere with the conduct of the study [70,71]. On the other hand, the HYVET trial, which assessed the effects of treatment of hypertension in a much older population of which the majority were Chinese and nonrepresentative of Caucasians, despite all its caveats, proved that it is not impossible to conduct randomized control trials in older people by enrolling patients over the age of 80 years to the study. The average age of the participants of this trial was 83.5 (SD \pm 3.2) years [72].

Trials in atrial fibrillation

Atrial fibrillation is one of the most common cardiac rhythm disorders seen globally. Approximately 70% of patients who suffer from atrial fibrillation are between the ages of 65 and 85 years [73]. The median age of 2.2 million people who suffer from atrial fibrillation is approximately 75 years [73]. The prevalence of atrial fibrillation varies from 0.1% in individuals <55 years of age to 9% in individuals >80 years of age [74]. A meta-analysis of 29 randomized control trials from 1996 to 2007, which included 28,044 participants assessing antithrombotic therapy with warfarin against aspirin, found that the mean age of the patients in these trials was 71 years representing mostly the younger spectrum of the vulnerable population [75]. However, the BAFTA trial, which studied 973 patients aged 75 years or over (mean age 81.5 years, SD \pm 4.2) with atrial fibrillation concluded that data support the use of anticoagulation therapy with warfarin for people aged over 75 who have atrial fibrillation, unless there are contraindications or the patient decides that the benefits are not worth the inconvenience [76]. Thus the conclusion of this trial not only demonstrates the benefit of an intervention to a specific disease but also expands to encompass the other often overlooked whole-person approach, which is vital in treating older patients. The trials that evaluated the place of newer oral anticoagulants in the recent past have included the healthier end of the population at risk. The AVERROSE trial, which compared the efficacy and safety of apixaban with those of aspirin, enrolled 5599 patients of whom the average age was 70 years [77]. The mean age of the enrolled 18,113 study participants of the RE-LY trial, which aimed to assess the effects of dabigatran compared with warfarin, was 71.5 with a SD \pm 8.6 years meaning

that only approximately 15% of the participants could have been above the 80 years [78]. In the ARISTO-TLE trial, which also had 18,201 participants studied to compare apixaban with warfarin for prevention of stroke or systemic embolization in patients with atrial fibrillation, the median age was 70 years with an interquartile range of 63-76 years [79]. The age range of the patients was not readily available with the results of the trial making it difficult to work out the age range of the upper quartile of the patients in this study. Similarly, the median age of the ROCKET-AF trial, which evaluated the efficacy of rivaroxaban compared against warfarin in 14,264 study participants was 73 years with an interquartile range of 65 to 78 years [80]. As in the ARISTOTLE trial, no age range of the study participants was mentioned with the results of this trial.

Stroke trials

On the other hand, some studies in acute ischemic strokes have been commendable in their approach and inclusion of older people. IST was a large, multicenter, randomized trial that recruited 19,435 patients and compared the effects of aspirin in acute ischaemic stroke against heparin with antithrombotic therapy given within 14 days; and suggested that aspirin should be commenced as early as possible after acute ischaemic stroke [81]. It did not have an upper age limit for enrolment and 25.5% of its participants were above the age of 80 years. Similarly, the IST-3 trial strived to answer the question whether there would be beneficial effects of intravenous thrombolysis administered within 6 h of the onset of stroke symptoms by enrolling 3035 patients, of whom 53% were in their 80s [82]. However, in an earlier trial (ECASS), which evaluated the effects of thrombolysis with recombinant tissue plasminogen activator in acute ischaemic stroke with the medication given within 3 h of onset of symptoms, the mean age of the participants was only 67 years [83].

Trials in other areas of medicine

Interventional randomized-control trials in areas of medicine other than cardiovascular disease also have not been immune from underrepresentation of older people. The average age of patients with hip fracture is 83 for women and 84 for men [84]. However, the FIT trial, which tested the hypothesis that 4 years of alendronic acid would decrease clinical and vertebral fractures in postmenopausal females who have low bone mineral density but without vertebral fractures, was on women only between the ages of 54 and 81 years and excluded women with 'medical conditions that preclude 3 years of participation' [85]. Another randomized trial that studied the effect of alendronate on risk of fracture in women with existing vertebral fractures, also enrolled a similar cohort of patients with a similar exclusion criteria [86]. A study designed to assess the effects of parathyroid hormone on fractures and bone mineral density in postmenopausal women with osteoporosis had no age boundaries however, the mean age of the study participants was 70 (SD \pm 7) years [87].

In Europe, the overall prevalence of Parkinsonism for the age groups 65-69, 70-74, 75-79, 80-84, and 85-89 years was 0.9, 1.5, 3.7, 5.0 and 5.1, respectively [88]. The corresponding age specific figures for Parkinson's disease were 0.6, 1.0, 2.7, 3.6 and 3.5 [88]. The average annual incidence rate of parkinsonism (per 100,000 person-years) in the age group 50-99 years was 114.7 with its incidence increasing steeply with age from 0.8 in the age group 0-29 years to 304.8 in the age group 80-99 years in a study conducted in Minnesota, USA [89]. Most studies suggest the mean age of onset of the disease is in the 70s [90]. Yet the mean age of the participants of the ADAGIO study, which used the delayed-start design to examine the potential diseasemodifying effects of rasagiline in Parkinson's disease in a cohort of 1176 subjects with untreated Parkinson's disease was 62 (SD ± 9.7) years with an age cut-off of 80 years [91]. The LARGO study was an 18 week, randomized, placebo-controlled, double-blind, doubledummy, parallel-group, multicenter trial undertaken in Europe with a view to investigating efficacy and safety of rasagiline in levodopa-treated patients with Parkinson's disease and motor fluctuations [92]. Although there was no specific age boundary, the study excluded patients with cognitive impairment (mini mental state examination score of ≤ 24), clinically significant or unstable vascular disease and clinically significant psychiatric illness, including major depression and the mean age of 687 study participants was 63 (SD \pm 9) years [92]. The ELLDOPA study assessed the effect of levodopa on the rate of progression of Parkinson's disease by enrolling 361 subjects, of whom the average age was 64.5 (SD \pm 10.9) years, patients with major depression and dementia had been excluded from this study as well [93]. A study that enrolled 179 patients with early Parkinson's disease to assess the effect of ropinirole on the incidence of dyskinesia compared with levodopa enrolled patients over the age of 30 years with no upper age limit. However, the average age of the participants of this trial was also 63(SD ± 9) years [94].

Research conducted in the UK demonstrated that the greatest incidence of diabetes occurs in patients over 60 years of age. In 1994 the incidence of diabetes was 5.20/1000 person-years in patients aged 65–69 years [95]. In 2003 it has doubled to 10.6/1000 person-years [95]. However the UKPDS trial, which enrolled 4075 newly diagnosed Type 2 diabetics to assess the relative efficacy of treatment for the disease over 3 years, enrolled only those who were aged 25-65 years [96]. The mean age of the recruits of this study was only 53 years [96]. The prevalence of diabetes in England had been found to be 5.1% with that of the whole of the UK little less than 5% [97]. Its prevalence according to age has been found to be 6 and 3.6% for men and women, respectively, in the age brackets of 45–54 years while it had been shown to be 15.7 and 10.4% for men and women, respectively in the ages between 65-74 years [97]. The figures are likely to reflect the prevalence elsewhere in the Western world. The ACCORD trial, which compared the effects of intensive treatment of diabetes with the standard treatment and had a mean follow-up duration of 1.2 years, had an age cut off at 79 years [98]. It recruited 10,251 patients, of whom the mean age was 62.2 (SD \pm 6.8) years [98]. It is clear that the representation of older people in clinical trials is poor and older people have been excluded from trials by either using age as a criterion or by introducing an exclusion criteria which affected them quite disproportionately than those who were younger.

Absence of adequate clinical trials in older people

Lack of adequate clinical trials in older patients that arrive at conclusions with regard to interventions for clinical conditions predominantly affecting older people is another salient shortcoming. On review of 22 trials, involving 2567 predominantly female and elderly patients, a Cochrane systematic review on anaesthesia for hip fracture surgery in adults, comparing regional anaesthesia with general anaesthesia, stated that there was insufficient evidence available from trials to arrive at a conclusion [99]. Another Cochrane systematic review, which included 23 trials involving 2861 patients, was unable to make definite conclusions on arthroplasties (with and without bone cement) for proximal femoral fractures in adults. It concluded that further wellconducted randomized trials were required, although cementing prostheses in place reduced pain postoperatively and resulted in better mobility and total hip replacement appeared to lead to a better functional outcome than a hemiarthroplasty [100]. Intramedullary nails for extracapsular hip fractures in adults had been systematically reviewed by Cochrane reviewers and the review included six studies, involving a total of 1071 predominantly female and older people with mainly unstable trochanteric fractures [101]. It concluded that there was limited evidence from the randomized trials undertaken up to then and data were insufficient to determine whether there were important differences in the outcomes between different designs of intramedullary nails used in the internal fixation of extracapsular hip fractures [101]. Given that the annual incidence of hip fractures in the UK alone is 70,000 [204], the dearth of data that comes to conclusions regarding treatment modalities of hip fracture can only be described as appalling and representative of the reluctance of researchers to enrol older people in clinical trials.

Reasons behind underrepresentation

In spite of the vast number of clinical trials performed over the years, which eventually led to development of management guidelines in almost all major noncommunicable diseases, the evidence base for intervention in older people who are most vulnerable to those diseases is patchy and incomplete. The evidence suggests that representation of older people in clinical trials up to now has not been in keeping with disease prevalence and incidence amongst them. It is clear that older people have either directly or indirectly been excluded from major clinical trials. Although age itself has been removed as an exclusion criterion lately in many trials, there seems to be other criteria in place that have enabled systematic exclusion of older people from clinical trials.

A recent analysis of 251 interventional (pharmacological or device-based) clinical trials in heart failure on the extent of exclusion of older individuals has recognised several poorly justified exclusion criteria in relation to the disease in question [102]. It was found that 25.5% of these trials have had an upper age limit. Exclusion by age was more common in trials conducted in the EU than those in the USA (32.3 vs 16.2%). However, the most common exclusion criteria were those based on comorbidity (in 80.1% of trials). Exclusion by specific comorbidities, such as renal or liver disease, was observed in 75.7%, whereas 10.4% excluded patients by comorbidity expressed in generic terms. In 36.3% of clinical trials, patients were excluded by reduced life expectancy. This exclusion criterion was more common in multicenter than in single-center trials. Some clinical trials (12.7%) have excluded patients because of cognitive impairment. This exclusion criterion was found to be more common in trials sponsored by public funding agencies. Exclusion by cognitive impairment was also more common in trials conducted in the USA than these in the EU. Approximately a fifth of the clinical trials on heart failure have excluded patients by concomitant use of drugs, and pharmacological trials had significantly higher rates of poorly justified exclusions of patients by this criterion than nonpharmacological interventional trials. Exclusion by physical impairment was observed in 13.9% trials. Most such trials did so by excluding patients who were unable to walk or to perform exercise testing. Inability to attend a followup visit was a reason for exclusion of patients in 9.6% of these trials. A systematic review of barriers to the recruitment of older patients with cancer onto clinical trials has also demonstrated that age was a significant barrier to recruitment; only a quarter to a third of potentially eligible older patients are enrolled onto trials [103]. Physicians' perceptions, protocol eligibility criteria with restrictions on comorbidity and functional status to optimize treatment tolerability were recognized as the most important reasons resulting in the exclusion of older patients in this review as well [103]. Other barriers included the lack of social support and the need for extra time and resources to enrol these patients [103].

However, these are not the only barriers for inclusion of older people in interventional clinical trials. Clinical medical research has always been based on quantitative rather than qualitative data and interpretation of results has been based on statistical terms and levels of significance even when the level of statistical significance may not be clinically worthwhile in terms of benefit rendered by the effects of intervention. This might have been observed in the trials of riluzole in motor neuron disease, where estimates from two of the trials suggest a gain in median tracheostomy-free survival of 2-4 months [104]. On the part of researchers there is always a desire to produce 'pure' results [105]. More pragmatic trials that might not yield 'clean' results therefore may be unappealing for researchers. In an economic climate where there could be a shortage of funding and where there could be more reliance on sponsorship of pharmaceutical industry, production of 'diluted' results might appear rather unacceptable to researchers or sponsors. Perception that older people are vulnerable and need protection from harm may also have deterred the researchers from recruiting them to clinical trials [105]. It is possible that failure on the part of researchers or sponsors to appreciate that outcomes are best measured in terms of quality of life as perceived by older people themselves and degree of independence rendered by the intervention studied in a clinical trial, rather than disease-free survival or death, may also have led to poor opportunities of participation for older people in clinical trials. Lack of clear definition as to what constitutes life-limiting illnesses or conditions may also have diminished the chances of older people getting involved in clinical trials given that 'old age' itself may be perceived as a life-limiting 'condition' by some researchers. In fact the PREDICT study, which gathered professional views from nine different countries in Europe, found that some researchers have felt that they were under no obligation to include older people in clinical trials and professionals in some countries have felt that it was justified to have age limits based on comorbidity (61-83%) and polypharmacy (63-85%) [106]. Some professionals have thought that having age limits on trial participation was justified because of reduced life expectancy (62%) and physical disability (58%) in older people [106]. Attitudes

of the professionals towards older people appears to be the greatest barrier for their inclusion in clinical trials.

Part of the blame may have to be shared by research ethics committees. Ethics committees do have a duty to point out to researchers that assent could replace consent where consent is not practical, however, the research question is still pertinent to those who have cognitive impairment and therefore lack capacity to consent for clinical trials. Similarly, research ethics committees could refuse approval of a clinical trial if there is apparent ageism or unjustifiable age cut-off in exclusion criteria of a research proposal. It is reasonable to expect that it is the responsibility of research ethics committees to pick up indirect age discrimination acting via unjustifiable multiple exclusion criteria in a trial which may disproportionately affect older people.

Some degree of laxity on the part of the regulators also seems to be contributory to the current state of affairs. A review carried out by the US Government Accountability Office on US FDA guidance and regulations related to data on elderly people in clinical drug trials found that medical officers involved in the new drug approval process are not required to report whether sufficient numbers of older adults have participated in clinical trials to assess the safety and effectiveness of new drugs coming up for approval [205].

The role and the influence of pharmaceutical industry in medical research cannot be overlooked or undervalued. Undoubtedly the sponsorship of the industry is a vital life-line for advancement of medical practice as it immensely contributes to evolution and evaluation of new medications. However, the fact that drug companies have been either willingly or unwillingly oblivious to systematic exclusion of older people who constitute their largest group of consumers from important trials designed to address vital clinical questions is unacceptable in the personal opinion of the authors of this article. Almost universal observation of underrepresentation of older people from large, multicenter clinical trials sponsored by pharmaceutical industry makes one believe that such exclusion is manoeuvred by the industry rather than by researchers. It is a clear social responsibility of drug companies to ensure that there is adequate and proportional representation of older people in major clinical trials that may result in a product of which the largest consumers would be the elderly population.

Future perspective

The future could be different for older people in medical research and clinical trials. It could be altered firstly by acknowledging and addressing the barriers currently in place for involvement of older people in medical research and then by being vigilant about potential new deterrents that may arise in the future. The future could also be changed by ensuring that there will be proportional representation of older people in clinical trials in keeping with the incidence and prevalence of diseases amongst them, rather than in proportion to their numbers in the population.

The current underrepresentation is now acknowledged in Europe and is being addressed. The PRE-DICT consortium which includes key European geriatricians, aims to investigate reasons for the exclusion of the elderly in clinical trials and to provide solutions for this problem [206]. It has drawn a PREDICT charter that is founded on recognition of the right of older people to access evidence-based treatment [207]. It stipulates the need to promote the inclusion of older people in clinical trials. It also addresses the need for existence of pragmatic clinical trials enabling participation of older people. The charter also states the need for safety of the elderly in clinical trials. It emphasises the importance of establishing alternative and pertinent outcome measures for clinical trials in the older population. It also recognizes the need for paying respect to the values of older people taking part in clinical trials.

The European Forum for Good Clinical Practice, a nongovernmental, nonprofiteering alliance of professionals involved in biomedical research, formed with a view to promoting high standards of quality in all stages of biomedical research, recently published its guidelines on medical research for and with older people in Europe [208]. This is a very comprehensive document defining the basic terminology and detailing the key concepts around legal and ethical issues pertinent to research in older people. It gives guidance on consent, assent, the role and composition of ethical committees and the role of geriatricians with regard to medical research. It also gives very clear direction on monitoring, defining end points and outcome measures along with guidance on conduct of pragmatic and; above all, safe research in older people.

In the authors' view, the role of regulatory bodies is no less important. At times, certain drugs can be authorized for use in age ranges well and above those used in clinical trials. There could well be a need to look at this issue separately before authorization is given for such use before 'benefit-extrapolation' is assumed. There may well be such internal assessment processes in place by key bodies such as the FDA and Medicines and Healthcare products Regulatory Agency in the UK, but some clarity on this issue would be a welcome step. Perhaps the regulatory bodies need to contravene drugs or procedures that have not been adequately studied in the oldest of older people. For example, alendronic acid is licensed in the UK without age restriction by the Medicines and Healthcare Products Regulatory Agency although the trials that established the efficacy of alendronic acid in prevention of osteoporotic fractures were confined to those who were under the age of 80–81 years [80,81]. Similarly, licence for enalapril in heart failure is not confined to those who are younger than 80 years of age, although the SOLVED trial, which established its efficacy in treatment of chronic heart failure, was limited to those who were under the age of 80 years [23]. Licence for bisoprolol for treatment of heart failure is not restricted to those who are under the age of 80 years, even though the CIBIS-II trial, which established its usefulness, was confined to those who were under the age of 80 years [23].

To see a difference in underrepresentation of older people, trial designs should be more conducive for participations of older people and should have a more pragmatic approach to research questions. This could be achieved either by conducting trials exclusively for older people with different or more pertinent outcome measures or by enforcing laws to ensure proportional representation of sectors of the population to which the question in research applies in clinical trials. Choosing more relevant end points in itself could improve the participation of older people in clinical trials. Evaluation of patients' ability to maintain independence and functionality as end points of an intervention may be more relevant to older people than the hitherto frequently favored end point of survival benefit of the intervention. In an economic climate where the funding for research is limited from nonprofit-making and nonpharmaceutical sources, stricter legislation to prevent discrimination against older people in medical research is perhaps the only way forward. The responsibility of making evidence-based medicine a reality for older people lies with all professional bodies that have the best interests of older people at heart.

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Executive summary

- The world has witnessed revolutionary changes in population growth and changing demographic trends, with rapid growth of older populations and an increased disease burden, many older people having significant comorbidity.
- The older population remains the largest group of medication users and hence there is a clear case for involving older people in clinical trials.
- Currently, older people are grossly underrepresented in interventional clinical trials.
- Such underrepresentation is evident in trials in cardiovascular disease, atrial fibrillation, and some other areas of medicine.
- In some areas of medicine, the evidence related to interventions in older people is completely lacking.
- There are many reasons for poor involvement of older people in clinical trials.
- There are several ways to improve their participation.

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