CHAPTER 1

The exclusion of older subjects from clinical trials: the PREDICT study

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Introduction

Clinical trials are considered the gold standard methodology to demonstrate the efficacy and safety of an intervention, whether it is a drug, a non-pharmacological treatment, or a multicomponent intervention. Although Avicenna, an eleventh-century philosopher and physician, in his book *The Canon of Medicine*, wrote the rules for experimental testing of drugs, the first true example of a clinical trial can be considered to be the experiment performed by James Lind in 1747. This scientist gave different acidic substances to sailors suffering from scurvy and found that those who ate oranges and lemons recovered from the disease after a few days. Nevertheless, the science of clinical trials is relatively young. The first example of a randomized trial is a study evaluating the effect of streptomycin in patients with tuberculosis, that was published in 1948 in the *British Medical Journal* [1]. In the past sixty years, clinical trial science has rapidly evolved in its theoretical and practical aspects [2]. However, clinical trials have developed following the dominant medical paradigm known as the "disease model" [3]. This implies that they are usually aimed at treating a specific disease with a specific treatment, avoiding, as much as possible, all the confounding factors that might interfere with the assessment of the efficacy and safety of the tested intervention. Therefore, clinical trials establish strict inclusion and exclusion criteria that select patients suffering only from the disease of interest and in need of no other treatment than that tested in the trial. However, these selection criteria tend to reduce the number of patients who are eligible to such an extent that those included are usually not representative of the patients who will be treated in clinical practice. This discrepancy between the trial population and the real-world

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population is widening as the aging of the population is accompanied by a higher prevalence of multimorbidity and, as a consequence, of multiple treatments, both with drugs and with non-pharmacological interventions (see Chapter 4). The results obtained in the context of the clinical trial often cannot be applied to the real-world patient population but only to a minority of subjects. In other words, the generalizability of trial results is decreasing and hence also the usefulness of the results to clinical practice. Older subjects, as well as children, are one of the most important categories that have suffered from this approach, often being excluded from clinical trials [4–6].

The elderly are the fastest-growing section of the population in almost every country in the world. Since most long-term conditions increase in prevalence with age, and older people take more medications than other groups, their exclusion from clinical trials has caused increasing concern. The efficacy, as well as the safety, of pharmacological and non-pharmacological treatments are often not well established in older patients. There is a risk that the evidence obtained in younger subjects if applied directly to older patients might not always be appropriate and in line with good clinical practice [7]. On the other hand, this situation may persuade some practitioners to avoid useful treatments in these subjects, leading to under-treatment, which is quite prevalent in the older population [8].

The PREDICT (Increasing the Participation of Elderly in Clinical Trials) study was funded by the European Union (EU) Seventh Framework program in 2008 with the aim of helping identify, address, and resolve the issues related to the exclusion of older people from clinical trials. This chapter will present and discuss the rationale and the most important findings of this project.

The exclusion of older people from clinical trials: a long-term issue

In the past twenty years, several studies have reported that older patients are under-represented in clinical trials that evaluate not only drug but also non-drug treatments for different conditions [9]. One of the first studies that highlighted this issue was undertaken by Gurwitz at the beginning of the 1990s [10]. The premise was that an increasing proportion of patients admitted to US hospitals with acute myocardial infarction were older subjects, while the patients included in clinical trials were significantly younger and more often men than women. The authors investigated the extent to which the elderly were excluded from trials of drug therapies used in the treatment of acute myocardial infarction performed before September 1991. They found that over 60% of trials excluded persons over the age of 75 years. Moreover, studies published after 1980 were more likely to have age-based exclusions compared with studies published before 1980. Finally, studies with age-based exclusions had a smaller percentage of women compared with those without such exclusions. Since the majority of

older subjects are women, this results in an even more pronounced limitation of the number of female older patients included in clinical research. A decade later, Lee and colleagues performed a new evaluation of clinical trials in acute coronary syndromes [11]. The authors conducted a thorough literature search of Medline and the Cochrane Database of Systematic Reviews from their beginning up to the year 2000. The included 593 unique cardiovascular randomized controlled trials (RCTs). The majority were multicenter and undertaken in a single country. Industry was the most commonly reported source of funding. More than 70% of trials enrolled fewer than 500 patients. Thrombolytic agents were the most common therapeutic class investigated, followed by antithrombotics. The majority of trials were performed in patients with myocardial infarction. The presence of explicit age exclusion criteria declined from 58% between 1966–1990 to 40% in the decade 1991–2000 and the percentage of patients older than 75 years increased in the same period from 2% to 9%. These changes represented an improvement compared with the findings of the previous study by Gurwitz, but still failed to a large extent to correct the under-representation of older people in these clinical trials.

More recently, van Spall *et al*. searched papers reporting RCTs in a number of conditions published between 1994 and 2006 in high impact factor medical journals, and extracted information on trial characteristics and patient exclusion [12]. In the context of each of 283 RCTs and the condition studied, the authors assessed whether exclusion was justified. The justified exclusions were classified as follows: (1) impossibility of granting of informed consent; (2) allocation to intervention or placebo group likely to harm the subject; (3) probable lack of effectiveness; or (4) the effect of intervention would be difficult to interpret. The researchers found that common medical conditions formed the basis for exclusion in 81.3% of trials while patients were excluded due to age in 72.1% of all trials (60.1% in pediatric populations and 38.5% in older adults). Moreover, individuals receiving commonly prescribed medications were excluded in 54.1% of trials. Surprisingly, only 47.2% of exclusion criteria were rated as strongly justified by Van Spall. Multivariable analyses revealed independent associations between the total number of exclusion criteria and drug intervention trials (risk ratio, 1.35; 95% confidence interval, 1.11–1.65; $p = .003$) and between the total number of exclusion criteria and multicenter trials (risk ratio, 1.26; 95% confidence interval, 1.06–1.52; $p = .009$). Industry-sponsored trials were more likely to exclude individuals due to concomitant medication use, medical comorbidities, and age. Drug intervention trials, compared to other type of trials (devise, surgery, and other) were more likely to exclude individuals due to concomitant medication use, medical comorbidities, female sex, and socio-economic status.

The exclusion of older patients from clinical research was also confirmed for several other common conditions of advanced age, such as heart failure [13, 14], cancer [15, 16], Alzheimer's disease [17], urinary incontinence [18], the evaluation of influenza vaccination [19], and diabetes [20].

Older people are excluded not only by putting arbitrary upper age limits in trial protocols [21, 22], but more often by means of indirect criteria, such as comorbidity, concomitant drug therapy, reduced life expectancy, nursing home residence, and perception of poor compliance. This implies that even when older patients are recruited in clinical research, they are usually healthier and less disabled than those suffering from the same condition living in the community or encountered in clinical practice [14, 23].

Causes and consequences of the exclusion of older people

The reasons underlying the exclusion of older subjects from clinical trials are many [24]. Some characteristics of older patients are considered potential issues for the design and conduct of clinical trials. Older participants are highly heterogeneous, in terms of physical health, cognitive function, and disability. Therefore, trial sponsors and investigators are concerned that their inclusion might dilute any active treatment effect and potentially lead to statistically non-significant results. The dropout rate is usually higher in trials involving older participants, due to a higher likelihood of becoming ill or dying during the trial, to relocation (institutionalization), or the unavailability of family members or caregivers to bring the older participants to the study site for follow-up evaluations. As a consequence, a larger number of subjects are likely to be required to enter the study in order to maintain adequate statistical power. The issue of obtaining informed consent is also important because of the high prevalence of neurological and psychiatric disorders in older participants [25]. Another issue that might explain the under-representation of older subjects is ageism, i.e. age-related discrimination [26]. Moreover, whenever a drug therapy is evaluated, there is always concern about the risk of drug–drug interactions, lower compliance, and adverse drug effects because of the multiple drugs patients are already taking. Other barriers include the need for extra time and resources to enroll older participants and keep them in the trial, with consequent higher costs. The perception of older people as a vulnerable population that might be endangered by the participation in research could also limit their inclusion. Although older participants are often willing to participate in clinical studies [27, 28], there is some evidence that lower educational attainment, low socio-economic status, the perception of excessive intrusiveness of the study in terms of collection of biological samples, duration of interviews, and transportation problems are all factors that might reduce their participation in research studies [24, 29].

The main consequence of the under-representation of older people in clinical trials is that the majority of drugs, as well as many non-pharmacological interventions, have been investigated only in few and usually highly selected older patients. This poses a challenge to the generalizability or external validity of their

results. The implication is that the value of many therapeutic interventions is not known in older subjects and healthcare professionals have to rely on studies performed on younger and healthier patients. However, since older people, and particularly the oldest subjects, i.e. over 85 years of age, are clearly different from younger adults, due to the interplay between aging, chronic diseases, polypharmacy, and lifestyle, there are inherent dangers in this forced necessity.

There is compelling evidence that the results of trials performed in younger adult populations cannot be automatically applied to older populations, both in terms of efficacy and safety. With regard to efficacy, the treatment of hypertension provides a clear example. While the treatment of systolic hypertension is beneficial in older adults, until a few years ago trials included only a limited number of participants aged 80 and older. The available data in this age group suggested that the pharmacological reduction of blood pressure decreased the risk of stroke but with a tendency toward a greater risk of mortality [30]. The pilot Hypertension in the Very Elderly Trial confirmed these ambivalent results [31]. On this basis, some experts opposed the treatment of high blood pressure in octogenarians [32]. Contrary to the expectations, a subsequent large trial provided evidence that treating hypertension reduces the risk of mortality from stroke, heart failure, and other cardiovascular diseases, as well as total mortality in a very old population, when patients were treated with the aim of achieving a target systolic blood pressure of 150 mmHg [33]. These results therefore demonstrate both that hypertension should be treated, at least in relatively fit older people aged 80 and older, as well as that the target for treatment is higher than in younger people.

Analogously, the inclusion of representative older patients is important to characterize the safety of a drug. A large randomized trial (Randomized Aldactone Evaluation Study, RALES) demonstrated that the use of spironolactone significantly improved outcomes in participants with severe heart failure [34]. Some years after its publication, there was a significant increase in the rate of prescriptions for spironolactone and also in hyperkalemia-associated morbidity and mortality [35]. One possible explanation for these findings is that patients treated in clinical practice were much older, usually female, and with higher prevalence of diabetes and renal failure, than those included in the RALES trial [36]. In essence, the lack of an appropriate evidence base for prescribing therapies in older patients makes the activity of physicians extremely complex and prone to the risk of both over-treatment and under-treatment.

The PREDICT study

As previously stated, older people account for high drug consumption, up to 60% in some countries, and they also often use non-pharmacological treatments but they have often been under-represented in clinical trials. PREDICT was the

Table 1.1 Participating centres and principal investigators in the PREDICT project.

Participant organization name	Country	Principal Investigator
Medical Economics and Research Centre Royal Hallamshire Hospital, Sheffield (Coordinator)	UK	Prof. David Edbrooke/Dr Gary Mills
Institute of Gerontology and Geriatrics, Department of Clinical and Experimental Medicine University of Perugia Medical School, Perugia	Italy	Prof. Antonio Cherubini
Keele Interdisciplinary Research Centre on Ageing (KIRCA). Institute for Life Course Studies, Keele University	UK	Prof. Peter Crome
Department of Internal Medicine and Geriatrics Sabadell	Spain	Dr Joaquim Oristrell Salva
Department of Nursing Home Medicine and EMGO Institute University Medical Centre Amsterdam	Holland	Prof. Cees Hertogh
Institute of Public Health, Krakow Jagiellonian University Medical College. Krakow	Poland	Prof. Katarzyna Szczerbińska
Geriatric Clinic Kaunas University of Medicine, Kaunas.	Lithuania	Prof. Vita Lesauskaite
Ana Aslan National Institute of Geriatrics, Otopeni	Romania	Prof. Gabriel Prada
Dept of Geriatrics Soroka Hospital, Ben-Gurion University Beer-sheva	Israel	Dr. Mark Clarfield
Department of Geriatrics First Faculty of Medicine, Charles University, Prague	Czech Republic	Prof. Eva Topinkova
Medical Research Council	UK	Dr Paul Dieppe

acronym used for the Increasing the Participation of Elderly in Clinical Trials project**.** This project was funded by the European Commission within the Seventh Framework program and it was undertaken between 2008 and 2010. The PREDICT partners were based in the Czech Republic, Israel, Italy, Lithuania, the Netherlands, Poland, Romania, Spain, and the United Kingdom and co-ordinated from MERCS, based in Sheffield, in the United Kingdom (Table 1.1). The aim of the project was to help identify, address, and resolve the issues related to the exclusion of older people from clinical trials.

The project was organized into five different work packages (WP). Work package 1 (WP1) was divided into two different parts: WP 1a was a systematic review of the literature to assess the extent of exclusion of the elderly from clinical trials in different conditions, chosen for their high prevalence and importance in older patients. WP 1b investigated ongoing clinical trials in heart failure to see whether the exclusion of older patients was still present in studies that would report in the years immediately after PREDICT had ended. WP2 and WP3 investigated the reasons why older people are under-represented in clinical trials and what can be done to improve their participation. In WP2, the opinion of professionals involved in clinical trials was sought by means of a questionnaire

while in WP3 patients and their carers were invited to participate in focus groups that explored their understanding, views, and opinions on this topic. WP4 aimed at developing, based on the findings of the other WPs, a Charter on the Rights of Older People to participate in clinical trials. WP5 was devoted to dissemination.

Work package 1a

This work package performed a systematic review of studies of older people and their representation in clinical trials with the aim of answering three main questions:

1. Are older people under-represented inappropriately in clinical trials for specified conditions?
2. What is the explanation of any under-representation of older people in trials?
3. How can the representation of older people in clinical trials be improved?

It was decided to investigate six conditions that are both prevalent and important in the older population. The conditions were dementia, colon cancer, heart failure, depression, hypertension, and the secondary prevention of coronary heart disease with statins. The systematic review was performed on the following databases: MEDLINE (1966 to Feb. 2008), EMBASE (1980 to Feb. 2008), ISI Web of Science (1900 to Feb. 2008), CINAHL (1982 to Feb. 2008), PsycINFO (1987 to Feb. 2008), ASSIA (1987 to Feb. 2008), the Cochrane Methodology Register, the Cochrane Database of Systematic Reviews, the HTA database on *The Cochrane Library*. Additional studies were identified by reviewing the reference lists of the identified articles. The search retrieved 5380 articles, of which 380 were identified as potentially relevant. The main findings of the review are reported here. The mean age of the participants in the heart failure trials was 61–63 years compared with the age at first diagnosis in clinical practice of 74–78 years. Nearly 30% of trials specifically excluded older people and fewer than 10% of trials included patients aged over 80 years. Patients enrolled in heart failure clinical trials tend to have more severe left ventricular failure, less comorbidity, and have coronary artery disease as the cause. In hypertension, it was found that the weighted mean age of patients in trials was 63.5 years. However, the age-specific incidence of hypertension reaches a maximum at ages 65–69 years and remains at this level until ages 80–84 years. Thirty percent of patients diagnosed with hypertension are aged 75 years or older and 44% are 70 years or older. Only one large trial has studied the treatment of hypertension in people aged 80 years or above. Trial participants tended to have fewer cardiovascular risk factors, comorbidities, and cardiovascular disease than the general older hypertensive population. In Alzheimer's disease, the mean age of the patients included in trials was less than 75 years. The age distribution of people with Alzheimer's disease is broad and for trials to be truly representative of the affected population, they should include a large proportion aged between 75 and 90 years. People participating in trials were more likely to be younger,

male, have a higher income, and have been educated to college level. In advanced colorectal cancer, the median age of patients included in trials was 62 years. This was considerably younger than the median age of diagnosis which in the period 1992–2001 was 70 years. Only 29% of trials had an upper age limit but several authors suggest that oncologists are uncomfortable enrolling older patients into trials.

Depression is one of the most common mental disorders in older people, and considering the demographic changes in the developed and developing countries, it is becoming a major public health problem [37]. From a clinical point of view, depression in older people is associated with functional decline, greater morbidity, increased risk of hospital admission, institutionalization, and overall mortality, due to increased risk of suicide and other causes, being responsible also for higher healthcare costs [38]. In this condition the evaluation of the literature did not provide clear evidence that older patients were under-represented.

Subsequently, the researchers searched for surveys, qualitative studies, and reports of trial experiences that have identified barriers to participation in clinical trials and factors that may improve or promote participation. This search was limited to studies in or at least including older people and which had appropriate methodology. The data was summarized in the form of a qualitative overview with no attempt to quantify the importance of each barrier or promoter. Barriers and promoters were divided into those pertaining to patients and those relevant to healthcare professionals. The barriers to participation that were identified by health professionals were: (1) absence of an obligation for pharmaceutical companies to conduct RCTs in older people; (2) perception of the implications of trial participation for the patient; (3) perception of the implications of trial participation for their clinical practice, and (4) physicians' views on the research topic. The barriers to participation identified by patients were: (1) unwillingness to compromise current care; (2) risk and fear of trial treatment; (3) problems with transport and access; (4) dislike of randomization and being experimented on; (5) time/scheduling conflicts; (6) financial implications; (7) the need to take care of dependents; (8) quality of information; (9) lack of interest; (10) poor self-rated health; and (11) concerns about information and consent.

The only factor identified by health professionals as a promoter was found in cancer patients, the involvement of a cancer specialist in recruitment, while the promoters of participation identified by patients were perceived health benefits, altruism, improved healthcare and understanding, financial incentives, and social interaction.

Table 1.2 shows strategies to improve participation of older people, subdivided into different aspects of clinical trial delivery.

Finally, the authors identified RCTs that attempted to improve recruitment or retention of older patients in RCTs. Only five trials were found, evaluating different interventions. One trial evaluated recruitment methods, two trials evaluated methods targeting consent procedures, one study targeted patient adherence,

Table 1.2 Strategies to improve participation of older people in clinical trials.

Commissioners and ethics committees
Eligibility criteria in clinical trials should be justified by trial designers
Trial design
Minimisation of exclusion criteria
Inclusion of patient preference arm
Larger sample size
Involvement of clinical staff in research design and implementation
Simplified protocols
Minimal demands on clinical and support staff
On-site coordination by clinical staff
Employment of data manager
Training for research staff
Conducting trials in well-established clinical settings
Comprehensive geriatric assessment
Recruitment process
Recruitment by specialized research staff/principal investigator/general practitioner/specialist clinic/older people/research nurse
Recognition and understanding of culture of different ethnic groups
Mass marketing and advertising
Follow-up of postal contact with a telephone call
Community outreach, health fairs, lectures
Personalized and face-to-face recruitment
Initial communication with trusted professional
Emphasize benefits of participation to others
Make expectations clear at initial contact
Easy physical access to research institutions
Provide transport or help arrange lifts, reimburse transport costs and parking
Offer home visit
Allow sufficient study time
Extended patient recruitment period
Financial incentives
Trial adherence
Be alert and responsive to potential signs of drop-out and problem solve
Remind of commitment, reiterate motivations, emphasize need for complete data
Minimize respondent burden and give control to participants
Give tangible support
Enlist support from relatives, friends, physician, and healthcare professionals
Establish best time to call, including evenings and weekends. Flexibility
Schedule study visits to coincide with other appointments (e.g. outpatient visit)
Frequent follow-up and contact
Individualize number of contacts, if perceived as too much of a burden
Reminder letters prior to visit
Home assessment visits
Offer phone/postal/e-mail/surrogate follow-up. Pay postage costs
Provide incentives or small tokens of appreciation, study specific items
Birthday/Christmas/thank you/illness cards
Newsletters/feedback on study

and one study aimed at improving professional compliance in a trial. No trial evaluated simple interventions to address barriers such as transportation issues, inconvenient timing, or care of dependents. Therefore, there is scanty evidence available on effective interventions to increase recruitment and retention of older participants in clinical research.

Work package 1b

There is a long time delay between the design of a clinical trial and the publication of its results. The aim of this WP was to investigate whether exclusion of older people is reducing as a consequence of a greater awareness of population aging and of a higher adherence of investigators to the recommendation provided by regulatory agencies to include older people in clinical trials [39, 40] (Box 1.1).

In order to address this research question, it was decided to analyze the characteristics of ongoing CTs by examining the online open-access CT registry platform maintained by the World Health Organization (WHO) [41]. The aims of this WP were to assess the extent of under-representation of older individuals in ongoing CTs, to evaluate the justifications for their exclusion, and to assess associations between trial characteristics and the exclusion criteria that have been applied. Heart failure was identified as a suitable target condition to study.

Older persons are more susceptible to develop heart failure (HF) due to the combination of age-related changes in the cardiovascular system and the high prevalence of cardiovascular diseases. Presently 80% of all cases of HF occur in persons aged 65 years and older [42] and, as a consequence of population aging, it has been estimated that the number of older adults with HF will sharply increase. For example, in the United States, this number is projected to double in the near future [43]. HF is also the main cause of hospital admission in this age group [44]. However, there is a dearth of research specifically targeting older

Box 1.1 Documents of drug regulatory agencies concerning older people in clinical trials issued before the PREDICT study

Since the late 1980s, the main regulatory agencies that oversee drug authorization in Europe (the European Medicine Agency, EMA) and in the United States (the Food and Drug Administration, the FDA) as well as the organization that includes the drug regulatory agencies worldwide (the International Conference of Harmonization, the ICH), have been aware of the paucity of information concerning the efficacy and safety of drugs in older adults. In 1989, the FDA first released official guidance on the study of drugs likely to be used in older adults [39]. This document clearly stated that advanced age should not be a barrier to participation in clinical trials and that study participants should reflect as much as possible the population that will receive the drug once marketed, i.e. "for drugs likely to be used in the elderly, older patients should be included in clinical trials in reasonable numbers." These principles were later adopted in an official ICH document [40].

HF patients. As already pointed out, about 30% of relevant clinical trials (CTs) excluded older persons and only 15% included patients aged over 80 years [13].

Information regarding ongoing CTs was obtained on December 1, 2008, from the WHO International Clinical Trials Registry Platform [41]. There were 378 registered trials recruiting patients with HF. A total of 127 studies were excluded: 79 because they had an observational design, 40 because they did not have HF as the main target condition, 6 because they investigated the physiopathology of HF, 1 because it was registered twice, and 1 because it involved children. Our analysis focused on the remaining 251 CTs (66.4%). Most CTs (220 = 87.3%) were extracted from the US registry (www.clinicaltrials.gov).

Most investigated non-pharmacologic interventions (156 = 62.2%), were performed in a single center (161= 64.1%), and were sponsored by public institutions (155 = 61.6%). We found that 64 CTs (25.5%) excluded patients by an upper age limit. This age varied between 65 and 95 years, with a median value of 80 years. The percentage of trials having this exclusion criterion was similar in the period 2002–2006 and in more recent years. Drug trials sponsored by public institutions had significantly higher rates of exclusion than drug trials sponsored by private entities. Moreover, exclusion by upper age limit was significantly more common in trials conducted in the European Union than in the United States. The most common exclusion criteria in the evaluated CTs were related to comorbidity (n = 201, 80.1% of CTs). Exclusion by specific comorbidities, such as renal disease, was observed in 190 CTs (75.7%), whereas 26 CTs (10.4%) excluded patients by comorbidity expressed as the presence of another generic disease.

In 91 CTs (36.3%), patients were excluded because of reduced life expectancy while drug therapy was an exclusion criterion in about one-fifth of the CTs (47 = 18.7%) and cognitive impairment in 32 (12.7%). Exclusion because of physical impairment was found in 35 CTs (13.9%). Standardized criteria were adopted to judge the appropriateness of exclusion criteria, based on a modification of methodology previously developed [12]. Applying these criteria, we found that almost half of the CTs (109 = 43.4%) had at least one poorly justified exclusion criterion, with similar proportions in pharmacologic and non-pharmacologic trials. In conclusion, the PREDICT study found that ongoing CTs, that will influence clinical practice in the field of heart failure in the near future, still discriminate against older individuals.

Work package 2

This WP aimed at collecting the opinion of relevant professionals about the exclusion of older people from clinical trials [45]. A structured questionnaire was administered to a convenience sample of six professional groups: geriatricians, general practitioners, nurses, clinical researchers, ethicists, and pharmacologists/pharmacists working in the pharmaceutical industry in nine countries (the Czech Republic, Israel, Italy, Lithuania, the Netherlands, Poland, Romania,

Spain, and the UK). A sample size of 540 professionals (almost ten from each of the six professions from each country) was considered adequate to provide an overall view and to offer an indication of inter-nation and inter-professional differences. A Delphi approach was used to develop the questionnaire using the information derived from the results of WP1a and WP1b. A pilot study was conducted in which the questionnaire was completed by two individuals from each professional group in each country (n = 46). The findings of this study were discussed in order to develop the final version which comprised three closed questions requiring a yes/no response and 43 questions asking respondents to rate their agreement/disagreement with a statement using a 6-point Likert scale. Furthermore, there was an opportunity to provide free-text supplementary responses. The questions investigated the under-representation of older people in clinical trials, the barriers to and promoters of the inclusion of older people in clinical trials, and potential improvements and regulation of clinical trials. Responses to the yes/no questions were analyzed as such. Responses to the Likert questions (strongly disagree, disagree, somewhat disagree, somewhat agree, agree, strongly agree)were dichotomized into either agree or disagree. A response rate of about 90% was achieved with 521 questionnaires returned. The detailed results are reported in the original paper [45]. The majority of respondents had previously been involved in clinical trials, the exception being nurses and GPs, of whom only 27% and 47%, respectively, had participated. Respondents believed that older people were under-represented in clinical trials (84%), that this under-representation caused difficulties for clinicians (79%) and that older people were disadvantaged as a result (73%). In answering questions about the justification of the exclusion criteria, about half of the responders believed that it might be justified to exclude older people in the clinical trial design, due to polypharmacy or comorbidity, while all the other criteria were not accepted by the majority of professionals. Only 18% agreed that it is possible to apply results obtained in younger patients to older patients and only 13% believed that upper age limits were justified. Nevertheless, the responders estimated that physicians would still be reluctant to recruit older patients, even in the absence of explicit upper age limits, mainly due to comorbidity, polypharmacy, risk of adverse drug reactions, and cognitive impairment.

In response to questions about promoters to the inclusion of patients for physicians, the majority of people questioned agreed that it would be important to make a specific requirement for the recruitment of older subjects, to set specific age-related recruitment figures and to offer an increased amount of money to those undertaking trials to take into account the potential extra work needed. At the patient level, some factors were deemed important by more than 90% of responders, for example, follow-up evaluations performed at home, encouragement by their doctors, simplification of trials, flexible appointments, reimbursement of transport costs, and staff using a reassuring manner when conducting trials. Slightly lower numbers supported other potential promoting

factors, such as entry recommended by a specialist, free care for treatment or follow-up, and if patients/carers regarded their participation as altruistic. Finally, the majority of respondents agreed that clinical trial sponsors would be more likely to recruit older people if they could receive appropriate financial compensation, for example, extension of the drug patent (87%) or if there were a legal requirement to include older people in clinical trials (88%). An extremely interesting finding of the survey is that about 70% of responders believed that the present arrangements for inclusion of older patients in clinical trials were unsatisfactory and 60% agreed with the statement that the regulation of clinical trials needed to be revised.

The study revealed some differences between healthcare professionals coming from different countries. Respondents from the older EU countries (Italy, the Netherlands, Spain, and the UK) often gave quite different answers compared with those from the other countries (the Czech Republic, Israel, Lithuania, Poland, and Romania). In essence, the exclusion of older people from clinical trials was considered more problematic and less justified by professionals from the old EU countries. Although a total of more than 500 responses were obtained, the number in each national professional group was small, and this together with possible subject selection bias means that inter-nation and group differences need to be interpreted with some caution. Nevertheless, it is possible that the views of health professionals in these different countries do reflect their diverse socio-economic backgrounds as well as their knowledge of clinical trials. Thus, respondents from the new member states of the EU which have in general younger populations and lower economic resources, might confer a lower priority to research studies performed specifically in the older population. Differences emerged between professional groups. Geriatricians were the most supportive of the need to change the current trial regulations whilst those coming from the pharmaceutical industry were the least keen to agree with this statement.

Work package 3

The aim of this WP was to understand older people's and their informal carers' views on whether or not older patients should be included in clinical trials [46]. More specifically, the research sought to explore whether there were particular conditions under which older patients should or should not be invited to participate, whether there were any identifiable barriers or facilitators to such participation, and whether people felt that any additional guidelines or legislation were necessary to support appropriate inclusion. The methodology chosen was a qualitative one, that is, the structured focus group method. This method allows for the exploration of a tightly defined topic by individuals involved in a particular situation and is suitable for topics that are not considered deeply personal. It also allows for the collaborative construction of meaning, encouraging exploration and debate within the group and is particularly suited to accessing lay knowledge [47].

It was decided to include older patients suffering from common diseases, such as cancer, cerebrovascular disease, dementia, depression, diabetes, heart failure, and carers of patients with dementia and cerebrovascular disease. Recruitment took place through existing patient groups in hospital settings and via community organizations working with older people. Only those considered able to give consent were invited to take part. After a pilot phase to refine the methodology, a total number of 42 focus groups were undertaken in the nine countries participating in the project, To assist in standardization across the partners, a video and protocol were produced detailing how to organize and run a focus group (www.keele.ac.uk/csg/downloads) in addition to a structured interview schedule, using questions which were formulated based on the findings of WP 1. Written information, together with consent forms, were sent in advance as part of the invitation to participate. The groups, which took place in the native language of each partner country, each had two facilitators. Discussions lasted approximately an hour and began with the written information about the study being explained orally. Discussants were invited to sign the consent forms, if they had not already done so, and consent was again checked at the end of the discussion. To maintain anonymity, discussants were allocated an alphabetic letter that replaced all names within the transcripts and identifying information was stored separately to transcripts. All focus groups were audio-recorded and transcribed.

Analysis took place at a number of discrete levels: a researcher from each partner country analyzed their data with a specific focus on the research questions as outlined in the interview schedule. A search was then performed for confirmatory or challenging evidence across and within all data sets.

The analysis of the focus groups led to the identification of four major themes: (1) ageism in society generally and among clinicians and researchers specifically; (2) awareness of advantages and disadvantages to participation; (3) the relationship between the participant and their clinician/research; and (4) practical features to support participation. Concerning ageism, the exclusion of older patients from clinical trials was seen as an expression of discrimination and linked to the ways in which older people are under-valued and less respected in society. Discussants were knowledgeable about the shift in demography and the importance of taking this into account in generating good science. Moreover, they were aware that the ageing process affects how an individual will respond to different drugs or therapies. Therefore, they were surprised that older people are often excluded from trials, also in view of the fact that age *per se* was generally not seen as a barrier. Nevertheless, age was considered as a sufficient reason to decline participation, and in some older people there was even an ageist attitude.

Participation in clinical research was not seen as without risk and caution was deemed necessary, particularly in frail older people where the risk of negative health outcomes might be increased. Linked to this was concern that participating in research such as clinical trials might disrupt existing, effective coping

and management strategies. Older respondents stated that outcome measures focused simply on extending life years were insufficient and that quality of life should be assessed. Motivating factors to becoming involved were related to perceived benefits to others and to oneself.

As far as consent was concerned, older patients declared that they valued the opinion of their doctor as the most important in influencing their decision. The physician in general was also seen as the most appropriate professional who should run clinical trials. This emphasis on the role of the physician was related to issues of safety and the importance of close scrutiny in both monitoring trials generally and the overall health of individual participants. The final decision on whether or not to take part should remain with the individual, or if that was not possible, with their family. Clear information was considered essential for consent, and it was felt that information was not always provided in an understandable form. A common complaint by participants who had taken part in research projects previously was the lack of feed-back about the results of the studies. Finally, discussants also mentioned some practical issues in being able to participate, as they realized that often they had to rely on relatives and care givers to support their participation and this imposed an additional burden on them. For some individuals this was a reason to decline taking part in clinical research. The location of the trial was also considered to be an important factor in an individual's capacity to take part, as was access to transport. For the majority of people having a trial located in a hospital gave an additional sense of security in emphasizing that they would be more closely monitored. However, for others, having to travel to participate was seen as a disadvantage.

Finally, respondents had contrasting opinions on whether a new legislation was needed and whether a Charter was useful to promote the participation of older people in clinical trials.

Work package 4: the Charter

The findings of WPs 1, 2 and 3 have been incorporated into a Charter which was produced through a Delphi process among the investigators and with independent advisors. The Charter was developed using six major principles that were identified from the findings of WP1, WP2 and WP3 (see Appendix1). The Charter was launched at British Medical Association House in London on February 1, 2010. It has been endorsed by the European Union Geriatric Medicine Society, the American Geriatrics Society, the British Geriatrics Society, the Gerontological Society of America, the Royal College of Physicians of London, the European Society of Anaesthesiologists, Age Platform Europe, the Association of Anaesthetists of GB and Ireland, the International Association of Gerontology and Geriatrics, the Italian Gerontological and Geriatric Society (SIGG), and the Italian Society of Pharmacologists (SIP).

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Appendix 1 The PREDICT Charter

1 OLDER PEOPLE HAVE THE RIGHT TO ACCESS EVIDENCE-BASED TREATMENTS

1.1 Older people have the right to be offered evidence-based treatments

1.1.1 Older people should expect to be offered drugs and other treatments that have been properly evaluated in clinical trials and demonstrated to be effective in people of their age.

2 PROMOTING THE INCLUSION OF OLDER PEOPLE IN CLINICAL TRIALS AND PREVENTING DISCRIMINATION

2.1 Older people should not be discriminated against in the recruitment for clinical trials

2.1.1 Older people should be informed about and invited to participate in clinical trials of treatments that are intended for use in older people.

2.1.2 National and International Regulators should ensure that older people are included in clinical trials without discrimination on grounds of age, gender, ethnicity, social class, religion or place of residence.

2.1.3 Research Ethics Committees, Sponsors, Medical Journal Editors and Regulators should review all studies critically for unjustified exclusions based on age, other illnesses, disability and existing drug treatment. All such exclusions must be justified.

2.2 The participation in clinical trials of people with multiple morbidities, frailty and disability should be encouraged

2.2.1 National and International Regulators should require that trials with drugs or other treatments intended for use in older people include those with multiple morbidities that are common in later life.

2.2.2 National and International Regulators should require that trials with drugs or other treatments intended for use in later life include older people who are taking commonly prescribed medications.

2.2.3 National and International Regulators should require that trials with drugs or other treatments intended for use in later life include older people who are disabled or in frail health.

3 CLINICAL TRIALS SHOULD BE MADE AS PRACTICABLE AS POSSIBLE FOR OLDER PEOPLE

3.1 Clinical trials should be designed so that older people can participate easily

3.1.1 Older people should receive information about clinical trials that helps them make an informed decision about participation.

Informed consent procedure should be adapted to the specific needs of older people, taking into account their level of literacy, any sensory deficits, and involving their family or caregiver if needed.

3.1.2 Specific training is needed in order to perform clinical trials in older people.

Researchers should be trained to conduct clinical trials in people with communication, sensory, mobility or cognitive problems.

3.1.3 Researchers should be prepared to spend additional time with older people participating in a clinical trial in order to support their participation and adherence.

3.1.4 Trial sponsors should recognize that older people may need extra support to take part in trials.

Trial sponsors should provide support to enhance the inclusion and adherence of older people, especially those with mobility and communication problems and those who also have responsibilities caring for others.

3.1.5 National and international regulators should encourage clinical trials that are designed to make the participation of older people easier.

4 THE SAFETY OF CLINICAL TRIALS IN OLDER PEOPLE

4.1 Clinical trials in older people should be as safe as possible

4.1.1 Researchers should assess the benefits and risks of older people's participation in clinical trials.

5 OUTCOME MEASURES SHOULD BE RELEVANT FOR OLDER PEOPLE

5.1 Clinical trials for common conditions in older people should employ outcome measures that are relevant for older people

5.1.1 *Researchers, trial sponsors and regulators should ensure that clinical trials for common conditions in older people use outcome measures that are relevant for older people, including quality of life measurements.*

5.1.2 *Clinical trial sponsors should involve older people and carers in the design of clinical trials and in the choice of outcome measures for clinical trials of diseases of later life.*

6 THE VALUES OF OLDER PEOPLE PARTICIPATING IN CLINICAL TRIALS SHOULD BE RESPECTED

6.1 The individual values of each older person participating in clinical trials should be respected.

6.1.1 Researchers should respect the values of each older person as an individual.

6.2 Older people should be able to withdraw from clinical trials without detriment to other treatments and their overall care.

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