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Barriers and potential solutions in the recruitment and retention of older patients in clinical trials – lessons learned from six large multi-center randomized controlled trials

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ABSTRACT

Background

Older people remain underrepresented in clinical trials, and evidence generated in younger populations cannot always be generalized to older patients.

Objective

To identify key barriers and to discuss solutions to specific issues affecting recruitment and retention of older participants in clinical trials based on experience gained from six current European randomized controlled trials (RCTs) focusing on older people.

Methods

A multidisciplinary group of experts including representatives of the six RCTs held two networking conferences and compiled lists of potential barriers and solutions. Every item was subsequently allocated points by each study team according to how important it was perceived to be for their RCTs.

Results

The six RCTs enrolled 7612 older patients. Key barriers to recruitment were impaired health status, comorbidities and diverse health beliefs including priorities within different cultural systems. All trials had to increase the number of recruitment sites. Other measures felt to be effective included the provision of extra time, communication training for the study staff and a re-design of patient information. Key barriers for retention included the presence of severe comorbidities and the

occurrence of adverse events. Long study duration, frequent study visits and difficulties accessing the study site were also mentioned. Solutions felt to be effective included spending more time maintaining close contact with the participants, appropriate measures to show appreciation and reimbursement of travel arrangements.

Conclusion

Recruitment and retention of older patients in trials requires special recognition and a targeted approach. Our results provide scientifically-based practical recommendations for optimizing future studies in this population.

Keywords: Clinical trials, recruitment, retention, barriers, older people, older patients

Keypoints:

- Older people remain underrepresented in clinical trials.
- Recruitment and retention of older patients in trials requires special recognition and a targeted approach.
- Our results provide scientifically-based practical recommendations for optimizing future studies in this population.

INTRODUCTION

Older patients, usually defined by an age of ≥65 years, remain underrepresented in clinical trials across most medical fields. [1-4] Evidence generated in younger populations cannot simply be generalized to older patients. [5] In the past, drugs approved with limited data derived from older people have caused unexpected adverse events in this population. Benoxaprofen, a drug for treating arthritis licensed in the 1980s, represents one inglorious example. Its product license was suspended shortly after approval because of increased rates of adverse reactions and deaths, especially among older patients. [6]

Underrepresentation of older patients in clinical research has been recognised for decades, [7] and efforts have been made to overcome this problem. For example, the PREDICT study funded by the European Commission not only explored the extent of exclusion and investigated the views of older patients and carers, but also developed a charter for improving the participation of older people in clinical trials [8, 9]. The EDICT initiative (United States) proposed practice and policy change recommendations for recruiting and retaining older patients into clinical trials [10]. Furthermore, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use published a guideline for research in older populations in 2013, as did the European Forum for Good Clinical Practice and the US Food and Drug Administration decades ago. [11-13] Despite these efforts, recommendations and guidelines, most trials continue to study populations that are substantially younger than their real-world counterparts [14]. Causes for the skewed age distribution are manifold and not limited to the often cited “upper age limit” exclusion criterion [15]

More research, and in particular more clinical trials, are needed to improve our evidence base for effective diagnosis, treatment, management and care of older people. This is particularly important in the light of the ageing population [16]. However, clinical trials enrolling older people face special challenges – especially with regard to recruitment and retention [17] – which require interdisciplinary solutions.

In 2014, the European Commission issued the Horizon 2020 research and innovation programme to ‘compare the effectiveness of existing healthcare interventions in the adult population’. As a result, six international multi-center randomized controlled trials (RCTs), designed for patients aged ≥ 65 years, were initiated (**Table 1**): GLORIA [18], SECURE [19], EU-CaRE [20], SITLESS [21], PRECIOUS [22], and OPERAM [23], with 7612 older patients currently enrolled in 20 countries.

In order to identify current barriers and challenges (apart from upper age limits) impeding the recruitment and retention of older patients in clinical trials, and to learn about potential solutions to

overcome these barriers, the GLORIA team initiated two networking conferences and conducted a survey within the six aforementioned international RCTs that explicitly focused on older patients.

METHODS

Networking Conferences

The Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis Study (GLORIA) included the objective of developing points to consider for clinical trials in older people. In order to discuss this, and to arrange ways to investigate the topic, a first networking conference was held in 2016, at a time when the six above-mentioned multi-center RCTs had just commenced. The conference brought together successful applicants to the Horizon 2020 call PHC-17, clinicians, epidemiologists and researchers in the field of trials for older people as well as patients. Several key points regarding potential barriers, challenges and potential solutions in study design and recruitment and retention of older patients in clinical trials were discussed. In addition, two systematic literature reviews (SLRs) on the topic were conducted and published [3, 17].

The multidisciplinary group met again in 2020 for a second networking conference. In the light of the experience gained during the conduct of the RCTs, the group exchanged first-hand experience regarding the hurdles that had to be overcome in the individual trials and the measures that were implemented to do so, and a survey to collect these experiences in a structured way was planned.

Survey

TB, NF and AP created a structured survey (**Appendix**) listing all statements drafted at both networking conferences by items in four sections: 1) challenges in recruitment; 2) solutions for challenges in recruitment; 3) challenges in retention; 4) solutions for challenges in retention. The survey was sent to the project leaders of the six RCTs. Together with the research staff responsible, they rated each item according to how relevant they perceived it to be for their RCT. They also had the option to add and rate further items. A total of 100 points were available to be distributed for each section. The more points an item got, the more relevant it was judged to be. Means were calculated to assess the importance of each item across all trials.

RESULTS

Barriers in recruitment

The results of our survey show that a main barrier in the recruitment of older patients in RCTs is perceived to be impaired health and the higher prevalence of acute or chronic comorbidities (**Figure 1**; 15.1 points). From the patient perspective, this may result in fear or unwillingness to accept or tolerate potential adverse events of study medication or intervention. From the viewpoint of the investigator, comorbidities are an obstacle not only because they can be prespecified exclusion criteria preventing participation, but also because they lead to additional time expenditure, increase the risk for adverse events, and may affect/confound treatment effects.

Moreover, we found that different health beliefs, different health care systems as well as differences in culture and priorities in older people were deemed relevant challenges for a uniform trial design and recruitment strategy in large international RCTs (14.7 points). Recruitment was frequently reported to be time-consuming and to require a high degree of flexibility (13.3 points). In addition, especially for patients living with frailty, travel and the logistics of study visits were mentioned as a major disincentive to participation. In this regard, the prospect of inadequate reimbursement of travel expenses was confirmed to have an additional negative impact on the recruitment yield (5.6 points).

Both scope and formulation of patient information were seen as another crucial barrier. Given the high prevalence of sensory and cognitive impairment in older people, a patient information that was too detailed, insufficient, or inappropriate hindered the recruitment.

General concerns about clinical trials and negative opinions of family members were perceived as having a relatively low influence on the recruitment (4.7 and 1,6 points respectively). Additionally, limited access to media or problems in dealing with smart devices was experienced as only a minor barrier in the recruitment process (1.3 points).

Solutions for challenges in recruitment

The proposal to increase the number of recruitment sites was well accepted across all six RCTs as it enhances the recruitment yield, especially when attempting to recruit harder to reach patient groups such as older patients (**Figure 2,** 14.2 points). Motivation and competition between the recruitment sites could be maintained by valuing successful recruitment teams, for example through appropriate awards/prizes (7.8 points). From the other side, investigators reported that early consideration should be given to closing recruiting centres with very low yield. The engagement of external recruitment agencies was not reported to be effective. In order to increase the number of patient referrals, sharing

information with other treating physicians was felt to be more effective (5.4 points) than using a variety of media (3.3 points).

Since there are several issues to consider for the recruitment and patient management in this target population, the increased expenditure of time observed in engaging with older patients should be accommodated by relieving responsible team members from other work at the study site (12.7 points). The offer of recruitment training to responsible site staff focussing on communication skills turned out to be an important proposal to optimize recruitment (10.2 points). It not only teaches the study staff how to engage successfully with older people but also helps to understand their priorities.

A measure that respondents considered very critical was the optimized design of the patient information This should be adapted to the needs of older people, i.e. be easy to understand whilst remaining scientifically sound (11.9 points).

Since cultural differences and differences in health care systems were identified as a major challenge in the recruitment process in the six RCTs examined, respondents felt that the design of clinical trials should take cultural habits and local needs into account (7.1 points) and incorporate best practices from other centres (mean score 7). Additionally, a central advisory board of stakeholders, including patients and caregivers, could be involved to find ways to make the trial less burdensome and to elaborate eligibility criteria and outcomes that align with older patients´ expectations and priorities (5.7 points).

Barriers in retention

Maintaining retention is often challenging in RCTs and depends on the disease/disorder under study and the general condition of the patient. However, numerous circumstances that occur more frequently at an older age were reported to affect retention of older people. Higher rates of comorbidities with high symptom burden, and frequent adverse events with hospitalization or even death resulting in missed visits and premature discontinuation were by far the most relevant causes for low retention rates. (**Figure 3,** 24.6 points). At the same time, higher rates of physical and/or cognitive impairment were perceived as making it more difficult for older patients to access the study site and its facilities (11.9 points), especially when they are dependent on support from other people.

Furthermore, it was perceived to be challenging to adapt the number and length of study visits to the needs of older participants without affecting the outcomes of the trial (13.6 points). Long study durations in particular are considered an important barrier to retention (14.7 points).

High turnover of the study staff was thought to have less relevance for retention of older people in the six RCTs conducted (5.6 points).

Solutions for challenges in retention

The study staff play an essential role in retention by keeping in touch with participants, valuing their contribution and making them feel that they "belong to a community" by sharing information with regular reports on study progress. Respondents supported sending these to the participants, their proxies, general practitioners (e.g. via newsletter and flyers) and other research teams (10.5 points). It was felt to be especially important for RCTs enrolling older people to maintain close contact by study personnel to allow early detection, understanding and management of adverse events and to meet their expectations (9.5 points). Sufficient time should be allowed for this at all trial visits (**Figure 4**). Aspects that were reported to negatively interfere with the patient-researcher-communication, e.g. interruptions during study visits should be avoided (14 points). However, a stable study staff complement was not perceived to be critical for better retention (4.6 points).

Trialists experience was that a success factor for retention was not only the expression of appreciation to participants through encouraging words, but also the investigator and study staff giving good reasons to continue the study (13.3 points). Other ways to express appreciation, such as monetary incentives or small gifts (e.g. tokens, vouchers, chocolate) were felt to be of lower influence on retention (1 point). However, travel arrangements (e.g. transport, lodging) should be made comfortable, and all travel expenses reimbursed in a timely manner (12 points).

In general, it was felt that sufficient leeway to adjust the duration and number of study visits to the patient´s needs should be provided (10 points). For especially frail patient groups, clinical trials should provide options to conduct home visits (7.9 points) or telephone follow-up visits to overcome the barriers of restricted access to the study site and its facilities.

A further measure for better retention suggested by some respondents was to offer free preventive medical check-ups and examinations during the clinical trial (9 points). This has the advantage to be convenient for older patients since it saves time and other expenses. Moreover, it helps the early detection or even prevention of adverse events that would otherwise hinder further participation.

DISCUSSION

This study provides first-hand experience from the investigators of six current large RCTs focused explicitly on older patients. It underlines that special measures should be applied to optimize study design, recruitment processes and retention rates, and why selection of eligibility criteria and outcomes in older people requires tailoring of study information and study protocols.

Our results show that the most limiting factor is time needed to address challenges in dealing with older people in RCTs. Older patients are known to suffer frequently from multiple comorbidities, take many medications and experience more drug-related adverse events [24, 25]. In accordance to our recent results and the findings of the PREDICT study [8, 17], these factors indeed represent very relevant barriers in both the recruitment and retention during the conduct of the RCTs examined.
The solutions should take into account individual priorities, appropriate valuation for participation including full reimbursement of all travel expenses, cultural differences and physical and/or cognitive impairment in order to improve study conduct in a way that allows motivated older patients to complete trials safely and without duress. These results are in line with the views of patients and their carers in the PREDICT study, who suggested i.e. assessments at home, simpler and fewer observations, help with travel and with carer responsibilities to make participation in clinical trials easier. The study staff plays a key role in communication and requires special education, which has also been highlighted by both the PREDICT study and EDICT study [8-10].
As the six RCTs examined were very heterogeneous in terms of their populations, interventions, study design, inclusion and exclusion criteria, it was not possible for us to analyse a relationship between the survey results and the exclusion criteria (**Appendix**).

The literature of recent years has highlighted that age-based exclusions in clinical trials limit the ability to generalize study findings to older patients with the highest morbidity and mortality [26, 27]. Apart from this, some review articles have addressed the underrepresentation of older patients by identifying barriers in the study design, recruitment and retention and proposed potential solutions. [15, 17, 28] A very recent meta-analysis showed that older people were underrepresented in trials of rheumatoid arthritis and osteoarthritis and similar evidence is presented from many other medical disciplines [3]. However, approaches to identify the most relevant barriers and to overcome these with practicable solutions remain very heterogeneous in their size and in the amount of detail reported, impeding adequate assessment of indicated barriers and solutions regarding recruitment and retention [17].

The strength of our work is that we used a unique approach to evaluate first-hand real-world evidence from six European Commission funded multicenter RCTs in different medical specialties with altered trial designs, enrolling almost 8000 patients aged ≥ 65 years. To the best of our knowledge, this is the first time a multidisciplinary group of experts in the field of research in older patients has examined their findings in this way for practical relevance based on the experience gained during the conduct of RCTs in this patient population.

The limitation is that the ratings in the questionnaires are mainly based on the assessments and experiences of the project leaders of the six clinical trials, even though all of them included members of the study team involved in the trials when awarding points to the items listed (to minimize the risk of bias). Because the trials were all pan-European, and responses were given on behalf of the whole trial by each team, comparison between countries was not possible. In addition, the results reflect the perspective of trialists, although patients contributed to the development of the survey at both networking conferences. Future studies should seek the perspective of patients and their care givers on how to make trials less burdensome.

A promising approach is the introduction of adaptive clinical trial design, which is very flexible and can investigate subpopulations with fewer participants [29]. It has already been successfully applied in COVID-19 studies [30]. The digitalization of clinical studies has also been pushed forward by the COVID-19 pandemic [31], this approach is currently being used successfully in COVID-19 trials and should set new standards for trial conduct [32]. It is perhaps reassuring to note that of the 3826 clinical studies currently underway on COVID-19, 3529 include patients aged ≥ 65 years [33].

In conclusion, the detailed analysis of the experience gained in six current large RCTs has identified the potential ways to overcome challenges in the recruitment and retention of older patients in trials. We hope our results facilitate a more focused approach to the planning and implementation of such studies. This will help to ensure that trials in older people deliver robust, relevant outcomes data that will appropriately influence clinical practice and hence improve the overall health of older people.

Table 1

Trial Acronym	Participants enrolled	Countries	Short description
GLORIA	451	Portugal, Germany, Italy, Slovakia, Hungary, Romania, The Netherlands,	Cost-effectiveness and safety of additional low-dose glucocorticoid in treatment strategies for older patients with rheumatoid arthritis
SECURE	2499	Spain, Italy, Germany, France, Poland, Hungary, Czech Republic	Efficacy of a polypill strategy containing aspirin, ramipril and atorvastatin compared with the standard of care in secondary prevention of major cardiovascular events in older patients with a recent myocardial infarction
SITLESS	1369	Spain, France, United Kingdom, Germany, Denmark	Exercise referral schemes enhanced by self-management strategies to battle sedentary behaviour in older adults
OPERAM	2008	Switzerland, Belgium, The Netherlands, Ireland	Optimising therapy to prevent avoidable hospital admissions in multimorbid older people
EU-CaRE	179 (RCT part)	Denmark, Spain, The Netherlands, France, Switzerland	Effectiveness and sustainability of current cardiac rehabilitation programmes in older people in Europe RCT: effectiveness of tele-rehabilitation in patients not (willing to) taking part in regular rehabilitation
PRECIOUS	Currently 1106	United Kingdom, Norway, Italy, Hungary, The Netherlands, Poland, Estonia, Germany, Greece	Assessment of prevention of aspiration, infections, or fever with metoclopramide, ceftriaxone, paracetamol, or any combination of these in the first 4 days after stroke onset to improve functional outcome at 90 days in older patients with acute stroke

Figure 1: Challenges in recruitment. Mean number of points awarded per item (standard error range: 0.17 – 9.17). The more points an item got, the more relevant it was perceived to be for the respective trial.

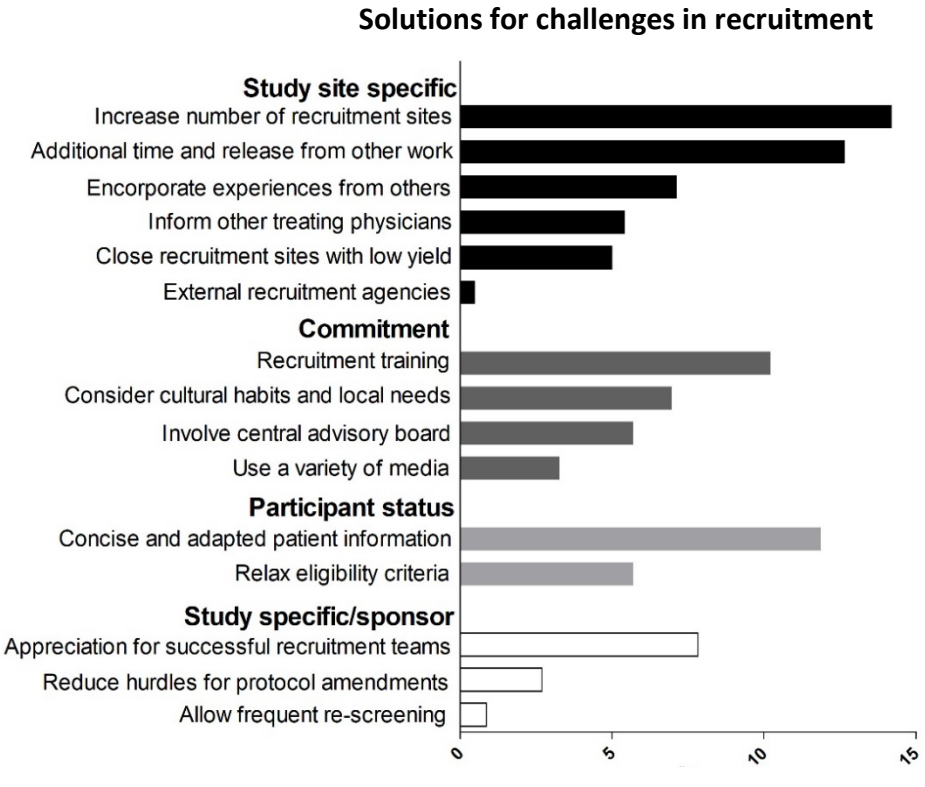

Figure 2: Solutions in recruitment. Mean number of points awarded per item (standard error range: 0.86 – 4,04). The more points an item got, the more relevant it was perceived to be for the respective trial.

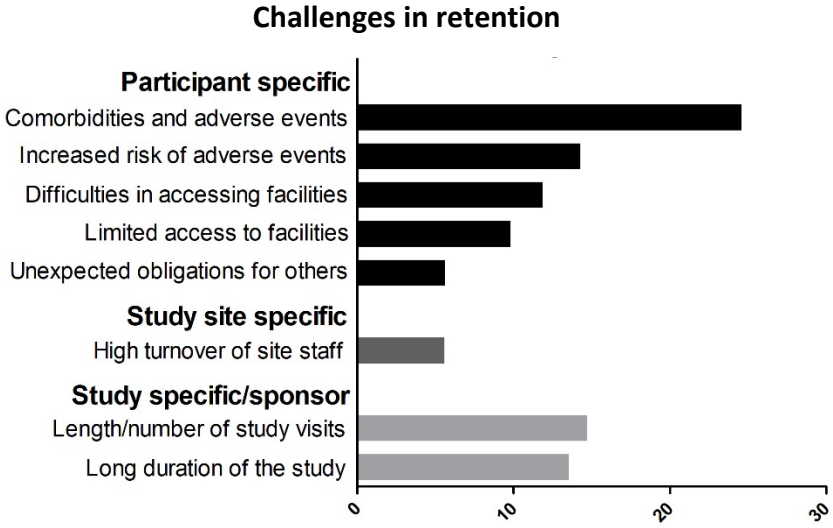

Figure 3: Challenges in retention. Mean number of points awarded per item (standard error range: 1,92 – 4,84). The more points an item got, the more relevant it was perceived to be for the respective trial.

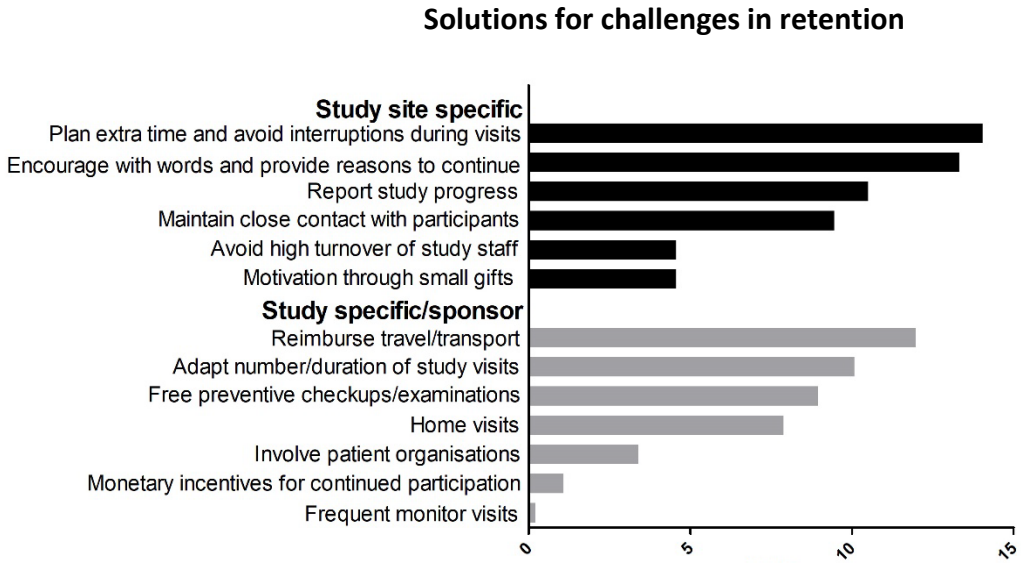

Figure 4: Solutions in retention. Mean number of points awarded per item (standard error range: 0,21 – 4,47). The more points an item got, the more relevant it was perceived to be for the respective trial.

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Declaration of Conflicts of Interest: None

Data Sharing

FB is willing to examine all requests for the full dataset during a period of 5 years from the date of this publication. The GLORIA steering committee will be involved in the case of query about access to data.

Transparency

The guarantor (FB) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

REFERENCES

1. Konrat C, Boutron I, Trinquart L, Auleley GR, Ricordeau P, Ravaud P. Underrepresentation of elderly people in randomised controlled trials. The example of trials of 4 widely prescribed drugs. PLoS One. 2012;7(3):e33559.
2. Broekhuizen K, Pothof A, de Craen AJ, Mooijaart SP. Characteristics of randomized controlled trials designed for elderly: a systematic review. PLoS One. 2015;10(5):e0126709.
3. Palmowski A, Buttgereit T, Palmowski Y, Nielsen SM, Boers M, Christensen R, et al. Applicability of trials in rheumatoid arthritis and osteoarthritis: A systematic review and meta-analysis of trial populations showing adequate proportion of women, but underrepresentation of elderly people. Semin Arthritis Rheum. 2019 Jun;48(6):983-9.
4. Schiphorst AH, Pronk A, Borel Rinkes IH, Hamaker ME. Representation of the elderly in trials of laparoscopic surgery for colorectal cancer. Colorectal Dis. 2014 Dec;16(12):976-83.
5. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". Lancet. 2005 Jan 1-7;365(9453):82-93.
6. Benoxaprofen. Br Med J (Clin Res Ed). 1982 Aug 14;285(6340):459-60.
7. Cotton P. Is there still too much extrapolation from data on middle-aged white men? Jama. 1990 Feb 23;263(8):1049-50.
8. Crome P, Lally F, Cherubini A, Oristrell J, Beswick AD, Clarfield AM, et al. Exclusion of older people from clinical trials: professional views from nine European countries participating in the PREDICT study. Drugs Aging. 2011 Aug 1;28(8):667-77.
9. Crome P, Cherubini A, Oristrell J. The PREDICT (increasing the participation of the elderly in clinical trials) study: the charter and beyond. Expert Rev Clin Pharmacol. 2014 Jul;7(4):457-68.
10. Herrera AP, Snipes SA, King DW, Torres-Vigil I, Goldberg DS, Weinberg AD. Disparate inclusion of older adults in clinical trials: priorities and opportunities for policy and practice change. Am J Public Health. 2010 Apr 1;100 Suppl 1(Suppl 1):S105-12.
11. International Conference on Harmonisation: Studies in Support of Special Populations: Geriatrics, current Step 4 Version. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E7/Step4/E7_Guideline.pdf (1993). Accessed Juni 2018.

12. US Food and Drug Administration: Study of Drugs Likely to be used in the Elderly. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/study-drugs-likely-be-used-elderly (1989). Accessed 15 Juli 2020.
13. European Commission: Medical Research for and with Older People in Europe. https://ec.europa.eu/eip/ageing/library/medical-research-and-older-people-europe_en (2013). Accessed Juni 2018 2018.
14. Nanna MG, Chen ST, Nelson AJ, Navar AM, Peterson ED. Representation of Older Adults in Cardiovascular Disease Trials Since the Inclusion Across the Lifespan Policy. JAMA Intern Med. 2020 Sep 8;180(11):1531-3.
15. Denson AC, Mahipal A. Participation of the elderly population in clinical trials: barriers and solutions. Cancer Control. 2014 Jul;21(3):209-14.
16. Eurostat. Aging Europe, Looking at the lives of older people in the EU, 2019 edition https://ec.europa.eu/eurostat/documents/3217494/10166544/KS-02-19-681-EN-N.pdf/c701972f-6b4e-b432-57d2-91898ca94893.
17. Forsat ND, Palmowski A, Palmowski Y, Boers M, Buttgereit F. Recruitment and Retention of Older People in Clinical Research: A Systematic Literature Review. J Am Geriatr Soc. 2020 Oct 19.
18. Hartman L, Rasch LA, Klausch T, Bijlsma HWJ, Christensen R, Smulders YM, et al. Harm, benefit and costs associated with low-dose glucocorticoids added to the treatment strategies for rheumatoid arthritis in elderly patients (GLORIA trial): study protocol for a randomised controlled trial. Trials. 2018 Jan 25;19(1):67.
19. https://clinicaltrials.gov/ct2/show/NCT02596126.
20. Prescott E, Meindersma EP, van der Velde AE, Gonzalez-Juanatey JR, Iliou MC, Ardissino D, et al. A EUropean study on effectiveness and sustainability of current Cardiac Rehabilitation programmes in the Elderly: Design of the EU-CaRE randomised controlled trial. European journal of preventive cardiology. 2016 Oct;23(2 suppl):27-40.
21. Giné-Garriga M, Coll-Planas L, Guerra M, Domingo À, Roqué M, Caserotti P, et al. The SITLESS project: exercise referral schemes enhanced by self-management strategies to battle sedentary behaviour in older adults: study protocol for a randomised controlled trial. Trials. 2017 May 18;18(1):221.
22. Reinink H, de Jonge JC, Bath PM, van de Beek D, Berge E, Borregaard S, et al. PRECIOUS: PREvention of Complications to Improve OUtcome in elderly patients with acute Stroke. Rationale and design of a randomised, open, phase III, clinical trial with blinded outcome assessment. European stroke journal. 2018 Sep;3(3):291-8.
23. Adam L, Moutzouri E, Baumgartner C, Loewe AL, Feller M, M'Rabet-Bensalah K, et al. Rationale and design of OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people (OPERAM): a cluster randomised controlled trial. BMJ Open. 2019 Jun 3;9(6):e026769.
24. Salive ME. Multimorbidity in older adults. Epidemiol Rev. 2013;35:75-83.
25. Hohl CM, Dankoff J, Colacone A, Afilalo M. Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. Ann Emerg Med. 2001 Dec;38(6):666-71.
26. Gurwitz JH, Col NF, Avorn J. The exclusion of the elderly and women from clinical trials in acute myocardial infarction. Jama. 1992 Sep 16;268(11):1417-22.
27. Bayer A, Tadd W. Unjustified exclusion of elderly people from studies submitted to research ethics committee for approval: descriptive study. Bmj. 2000 Oct 21;321(7267):992-3.
28. Carroll CB, Zajicek JP. Designing clinical trials in older people. Maturitas. 2011 Apr;68(4):337-41.
29. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry.
30. Ader F. Protocol for the DisCoVeRy trial: multicentre, adaptive, randomised trial of the safety and efficacy of treatments for COVID-19 in hospitalised adults. BMJ Open. 2020 Sep 21;10(9):e041437.
31. Inan OT, Tenaerts P, Prindiville SA, Reynolds HR, Dizon DS, Cooper-Arnold K, et al. Digitizing clinical trials. NPJ Digit Med. 2020;3:101.

32. Xue JZ, Smietana K, Poda P, Webster K, Yang G, Agrawal G. Clinical trial recovery from COVID-19 disruption. Nat Rev Drug Discov. 2020 Oct;19(10):662-3.
33. https://clinicaltrials.gov/ct2/results?cond=COVID-19: accessed November 4.