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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

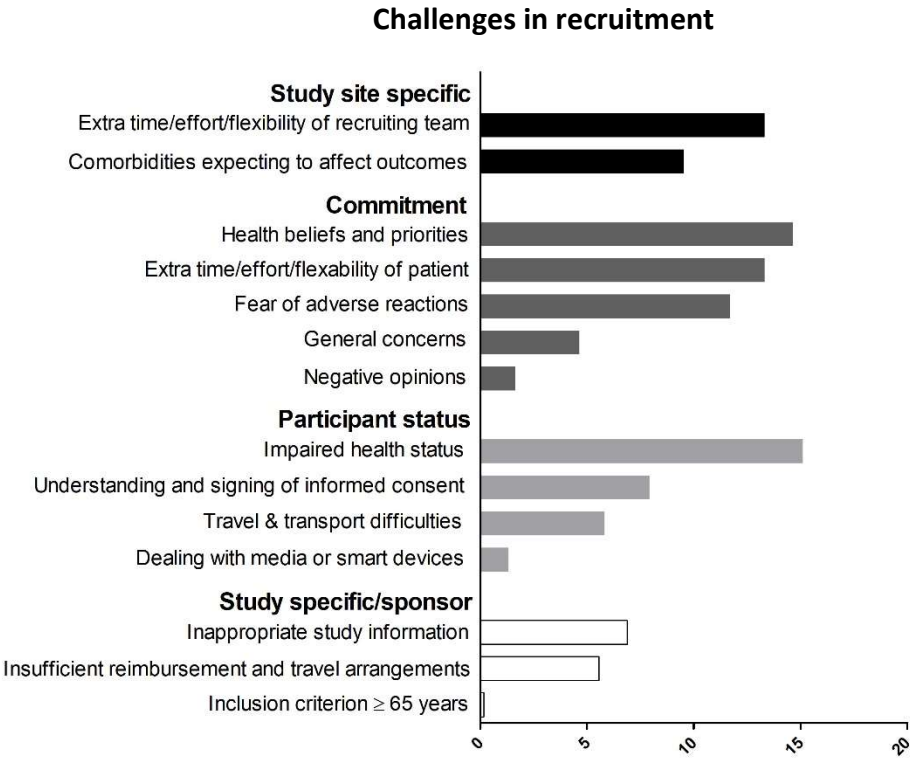

Figure 1: Challenges in recruitment. Mean number of points awarded per item (standard error range: 0.17 – 9.17). The more points an item got, the more relevant it was perceived to be for the respective trial.

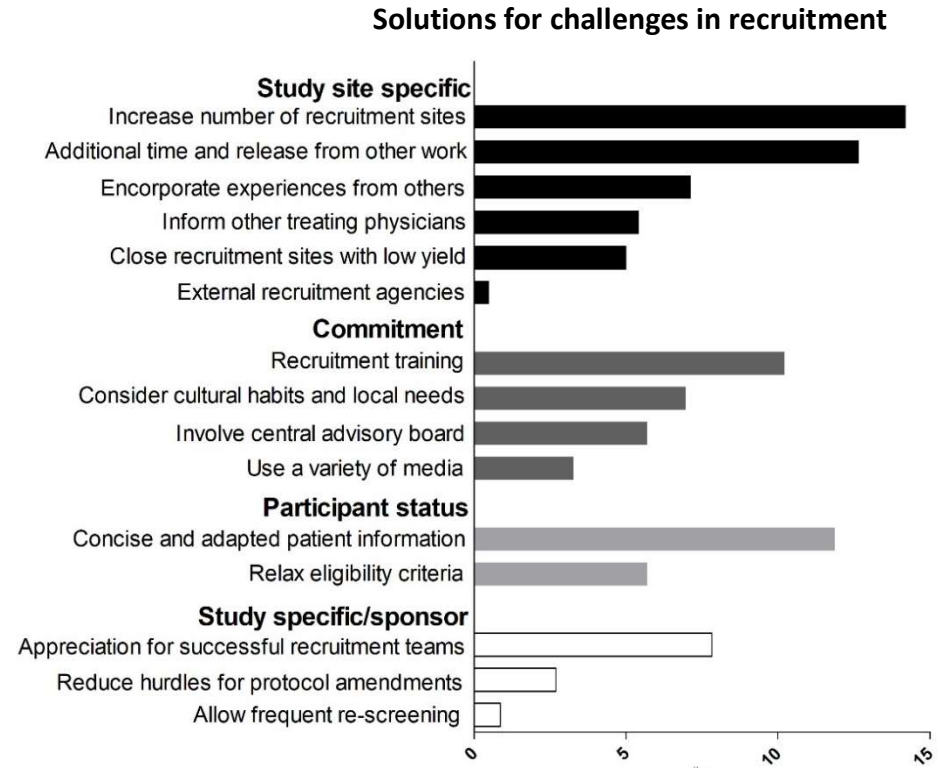

Figure 2: Solutions in recruitment. Mean number of points awarded per item (standard error range: 0.86 – 4,04). The more points an item got, the more relevant it was perceived to be for the respective trial.

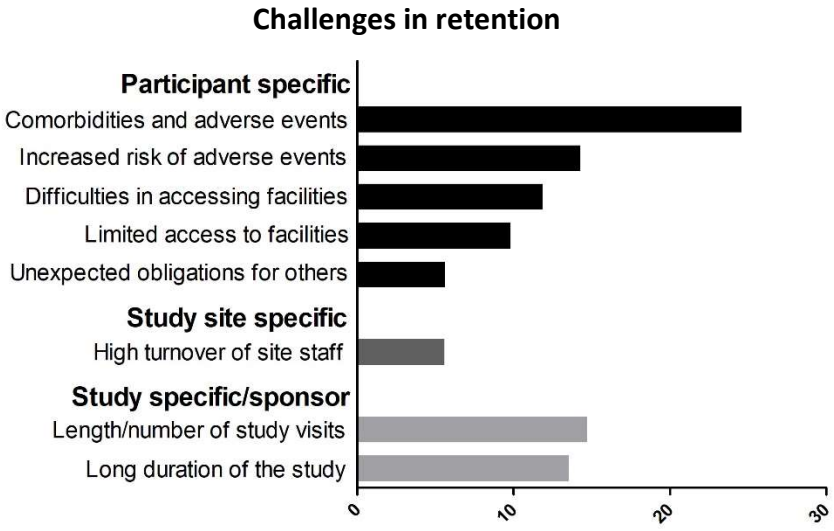

Figure 3: Challenges in retention. Mean number of points awarded per item (standard error range: 1,92 – 4,84). The more points an item got, the more relevant it was perceived to be for the respective trial.

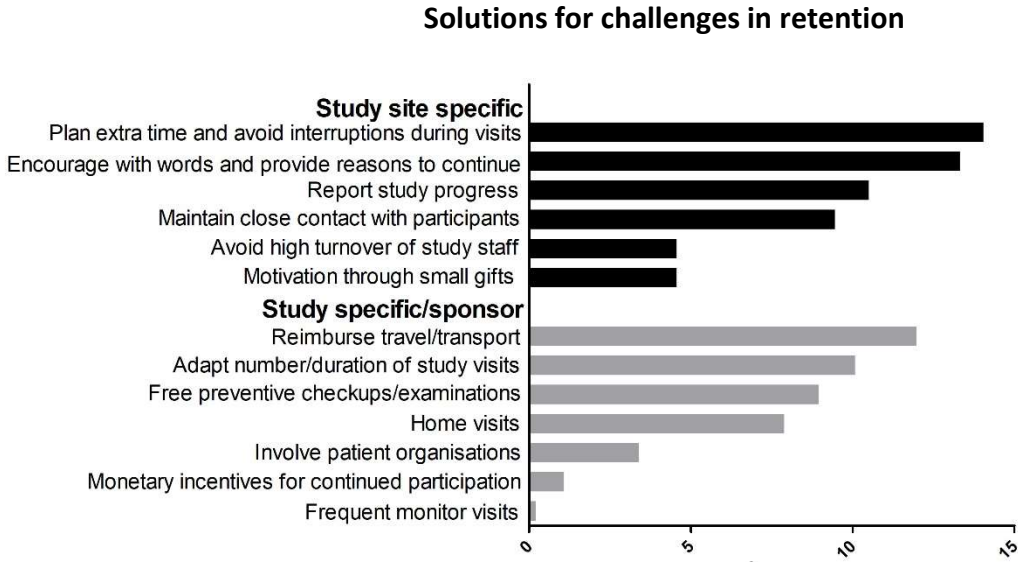

Figure 4: Solutions in retention. Mean number of points awarded per item (standard error range: 0,21 – 4,47). The more points an item got, the more relevant it was perceived to be for the respective trial.

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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.

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Supplement

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

Content:

1. Survey

The descriptions and corresponding tables listed were sent to the project leaders as Microsoft® Excel® documents.

Challenges in recruiting older people for clinical trials

Dear principal investigator, sub-investigator and/or site staff,

Please, first read the items listed below thoroughly. We have listed these items as potentially being the most important challenges in recruiting older people for clinical trials. These items were identified as a result of a systematic literature search and confirmed at our 2nd Networking Meeting.

Your task is to rate every item according to how relevant you perceived it to be for your Horizon 2020-funded trial. A total of 100 points must be distributed.

The more points an item gets the more relevant you perceived it to be. If in your opinion a challenge in recruiting older people has not been mentioned, please write it on the extra line and evaluate it accordingly.

Item	Rating points
1. Perceived or verified impaired general health status, acute or chronic comorbidity.	
2. Comorbidities expected to affect outcome measures.	
3. Cognitive impairment hindering understanding or signing of the informed consent.	
4. Fear of, or unwillingness to accept possible adverse effects of study medication or intervention.	
5. General concerns about clinical trials.	
6. Poor access to and problems dealing with media or smart devices.	
7. Extra time/effort/flexibility of the patient and recruiting team to make participation.	
8. Patient information is too detailed, insufficient or uses unfortunate wording.	
9. Insufficient reimbursement of travel arrangements or lack of monetary incentives.	
10. Health beliefs, health care systems, cultural differences and priorities of older people.	
11.	

TOTAL	**0,00**
MISSING	100,00

Solutions for challenges in recruiting older people into clinical trials

Dear principal investigator, sub-investigator and/or site staff,

Please, first read the items listed below thoroughly. We have listed these items as potentially being the most important solutions for challenges in recruiting older people into clinical trials. These items were identified as a result of a systematic literature search and confirmed at our 2nd Networking Meeting.

Your task is to rate every item according to how relevant you perceived it to be for your Horizon 2020-funded trial. A total of 100 points must be distributed.

The more points an item gets the more relevant you perceived it to be. If in your opinion a solution for challenges in recruiting older people has not been mentioned, please write it on the extra line and evaluate it accordingly.

Item	Rating points
1. Involve a variety of media to reach both potential study participants and family members.	
2. Involve a central advisory board that includes both patient representatives and caregivers to elaborate outcomes that align with priorities and expectations of older people.	
3. Design recruitment strategies that take cultural habits and local needs into account.	
4. Design patient information that is concise, scientifically sound, easy to understand and adapted to the needs of older people.	
5. Offer recruitment training to site staff focusing on communication skills with older patients.	
6. Consider additional time for the study team to conduct the study and relieve them from other work.	
7. Design recruitment strategies that incorporate experiences and success factors from other centers.	
8. Engage external recruitment agencies.	
9. Inform other treating physicians.	
10. Increase the number of recruitment sites.	
11. Close recruitment sites with low recruitment yield.	
12. Express appreciation for successful recruitment teams through appropriate awards.	
13. Relax eligibility criteria.	
14. Allow frequent re-screening.	

15. Reduce hurdles for protocol amendments.	
16.	

TOTAL	**0,00**
MISSING	100,00

Challenges in the retention of older people in clinical trials

Dear principal investigator, sub-investigator and/or site staff,

Please, first read the items listed below thoroughly. We have listed these items as potentially being the most important challenges in the retention of older people in clinical trials. These items were identified as a result of a systematic literature search and confirmed at our 2nd Networking Meeting.

Your task is to rate every item according to how relevant you perceived it to be for your Horizon 2020-funded trial. A total of 100 points must be distributed.

The more points an item gets the more relevant you perceived it to be. If in your opinion a challenge in retention of older people has not been mentioned, please write it on the extra line and evaluate it accordingly.

Item	Rating points
1. Increased risk of adverse events.	
2. Comorbidity (physical or cognitive impairment) and adverse events (especially hospitalization or death) causing missed visits and premature discontinuation.	
3. Long duration of the study.	
4. Length and number of study visits.	
5. High turnover of the site staff.	
6. Difficulty in accessing the study site and its facilities.	
7. Unexpected care for a sick spouse, friend or relative.	
8. Limited access to the study center and facilities of the study site.	
9.	

TOTAL	**0,00**
MISSING	100,00

Solutions for challenges in the retention of older people in clinical trials

Dear principal investigator, sub-investigator and/or site staff,

Please, first read the items listed below thoroughly. We have listed these items as potentially being the most important solutions for challenges in the retention of older people in clinical trials. These items were identified as a result of a systematic literature search and confirmed at our 2nd Networking Meeting.

Your task is to rate every item according to how relevant you perceived it to be for your Horizon 2020-funded trial. A total of 100 points must be distributed.

The more points an item gets the more relevant you perceived it to be. If in your opinion a solution for the retention of older people has not been mentioned, please write it on the extra line and evaluate it accordingly.

Item	Rating points
1. Report study progress regularly to research teams, associated physicians, participants and their families (e.g. via newsletters, flyers, cards).	
2. Reimburse travel.	
3. Provide monetary incentives to patients for continued participation.	
4. Express appreciation to study participants with encouraging words, and provide them with good reasons to continue the study.	
5. Plan extra time for each trial visit, and avoid interruptions during the visit.	
6. Adapt the duration and number of study visits to the patient's needs.	
7. Consider home visits.	
8. Avoid high turnover of the site staff.	
9. Maintain close contact with the study participants to allow early detection, understanding and management of adverse events.	
10. Involve patient organizations to understand and meet the older patient's needs.	
11. Motivate study participants through small gifts (e.g. chocolate, vouchers, tokens)	
12. Offer free preventive medical checkups and examinations during the study.	
13.	

TOTAL	**0,00**
MISSING	100,00

2. Exclusion criteria

GLORIA

Exclusion criteria: these criteria are categorised as having low probability of benefit, having high probability of harm, difficulty in measuring benefit and/or harm, and patients not capable of or willing to provide informed consent.

1. Having low probability of benefit

a. Change, stop or start of antirheumatic treatment in the last month prior to eligibility assessment, including methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, azathioprine, intramuscular and oral gold, cyclosporine, biologic agents including anti-tumour necrosis factor (TNF), anakinra, abatacept, rituximab, tocilizumab

b. Treatment with systemic glucocorticoid (GC): oral or parenteral GC with a cumulative prednisolone equivalent c. Treatment with any GC (oral, intra-articular, intravenous or intramuscular) in the last 30 days

2. Having high probability of harm

d. Exposure to investigational therapy in the last 3 months
e. Current participation in another clinical trial
f. Major surgery, donation, or loss of approximately 500 ml blood within 4 weeks prior to the screening visit
g. Absolute contraindication to low-dose prednisolone, as determined by the treating physician, such as: uncontrolled chronic infections, diabetes mellitus, hypertension, osteoporosis. When these conditions are under control (e.g. with anti-osteoporosis drugs, antihypertensive drugs) these patients can enter
h. Absolute contraindication to calcium and/or vitamin D supplement as determined by the treating physician, such as hyperparathyroidism (when insufficiently treated)
i. Uncontrolled comorbidities, short life span, etc. as determined by the treating physician

3. Difficulty in measuring benefit/harm

j. Absolute indication to start with oral or intravenous GC, according to the treating physician
k. Inability to comply with medical instructions or inability to assess major outcomes

4. Not capable or willing to provide informed consent

Most exclusion criteria are temporary

SECURE

1. Unable to sign informed consent.
2. Contraindications to any of the components of the polypill.
3. Living in a nursing home.
4. Mental illness limiting the capacity of self-care.
5. Participating in another clinical trial.
6. Severe congestive heart failure (NYHA III-IV).
7. Severe renal disease (Creatinine Clearance (CrCl) <30ml/min/1.73 m2).
8. Need for oral anticoagulation at the time of randomization or planned in the future months.
9. Any condition limiting life expectancy <2 years, including but not limited to active malignancy.
10. Significant arrhythmias (including unresolved ventricular arrhythmias or atrial fibrillation).

11. Scheduled coronary revascularization (patients can be randomized after final revascularization is completed within the prespecified timeframe).
12. Do not agree to the filing, forwarding and use of his/ her pseudonymised data.

EU-CaRE

- Contraindications to Cardiac Reabilitation (CR)
- Mental impairment leading to inability to cooperate
- Severe impaired ability to exercise
- Signs of severe cardiac ischaemia and/or a positive exercise testing on sever cardiac ischaemia
- Insufficient knowledge of the native language
- Implanted cardiac device (CRT-P, ICD)

SITLESS

Participants will be excluded if they: (1) have moderate or severe dementia when screened with the six-item screener to identify cognitive impairment, using a cutoff of three or more errors (2) have a medical condition which may interfere with the study design; (3) have unstable medical conditions (e.g. elevated blood pressure after medication, uncontrolled hypertension) or symptomatic cardiovascular diseases that contraindicates participation in Physical activity; (4) expect not to be able to attend 75% of the exercise referral schemes (ERS) sessions throughout the intervention; and (5) have participated in an ERS in the six months prior to their entry into the study.

PRECIOUS

1. Active infection requiring antibiotic treatment;
2. Pre-stroke score on the mRS 4b 3. Death appearing imminent at the time of assessment Criteria for censoring a treatment stratum: For the metoclopramide stratum: 1. Hypersensitivity to metoclopramide or to any of the excipients; 2. Gastrointestinal haemorrhage, mechanical obstruction or gastro-intestinal perforation for which the stimulation of gastrointestinal motility constitutes a risk;
3. Confirmed or suspected pheochromocytoma;
4. History of neuroleptic or metoclopramide-induced tardive dyskinesia;
5. Epilepsy;
6. Parkinson's disease;
7. Use of levodopa or dopaminergic agonists;
8. Known history of methaemoglobinaemia with metoclopramide or of NADH cytochrome-b5 deficiency.
9. Clinical indication for the use of metoclopramide. Incidental use of metoclopramide before screening is not an exclusion criterion.
For the ceftriaxone stratum: 1. Known hypersensitivity to beta-lactam antibiotics; 2. Clinical indication for antibiotic treatment. The use of an antibiotic before screening is not an exclusion criterion. For the paracetamol stratum: 1. Known hypersensitivity to paracetamol or any of the excipients; 2. Known severe hepatic insufficiency; 3. Chronic alcoholism; 4. Clinical indication for the use of paracetamol. Incidental use of paracetamol before screening is not an exclusion criterion.

OPERAM

"Exclusion criteria are reduced to a minimum to allow for maximum generalisability. Only patients planned for direct admission to palliative care (24hours after admission), or patients undergoing a structured drug review other than the trial intervention, or who have passed a structured drug review within the last 2months are deemed ineligible."