


Recruitment and Retention of Older People in Clinical Research: A Systematic Literature Review

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See related editorial by Robison et al. in this issue.

OBJECTIVE: To identify barriers and solutions for the recruitment and retention of older (aged ≥ 65 years) people in clinical trials.

DESIGN: Systematic literature review.

METHODS: Three databases (Medline, Embase, and CENTRAL) were searched for articles reporting on barriers or solutions regarding the recruitment or retention of older people. Only original research articles were included.

RESULTS: Fifty eligible articles were identified. Exclusion criteria were the most common cause of poor recruitment of older adults (mainly age and comorbidities). Patients' families or physicians often advised against participation (22% of included studies). Lack of interest (18%) and problems with transportation (18%) were also commonly cited as challenges. Fourteen trials (28%) reported that monitoring and adapting their recruitment methods helped, along with a flexible research team (26%) and provision of transportation (24%). Retention was impaired by death (12%), illness (8%), and loss of interest (6%). Methods with a positive effect on retention included financial incentives and regular information about the progress of the study (12%), a low staff turnover (12%), flexibility in appointment making (10%), and expression of appreciation by the staff through letters, gifts, and cards to the participants (10%).

CONCLUSION: We identified several barriers and have listed potential solutions that may improve recruitment and lead to fewer dropouts in trials involving older populations. Implementation of our findings may help mitigate the manifold challenges that come with running a trial with older people. *J Am Geriatr Soc* 68:2955-2963, 2020.

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INTRODUCTION

Older adults (commonly defined as being ≥ 65 years old)¹ are underrepresented in clinical research in virtually all medical fields,²⁻⁸ and medical guidelines commonly rely on trials that did not include sufficient numbers of such patients, potentially reducing their applicability in this age group.⁹⁻¹¹ For example, medication successfully tested in younger patients can induce unexpected adverse effects in older individuals.^{12,13} To ensure safety and efficacy of interventions in older people, they should not be excluded from trials.

Underrepresentation of older adults in clinical trials may be caused by several factors: Researchers often set arbitrary age limits¹⁴⁻¹⁸ for ethical considerations¹⁹ or are concerned about frailty.²⁰⁻²³ However, even studies that report no explicit exclusion of older people by chronological age do not include enough older participants.^{4,24-26}

The literature on the willingness of older adults to participate in research is contradictory: Some studies found that willingness to participate decreased with age,²⁷ but in others, older people were described as curious and interested in research.^{28,29} Increased prevalence of comorbidities and health issues related to age, lack of transportation, impaired understanding of the consent form, distrust in research, and seeing no relevance or benefit in the study were listed as further barriers to participation and retention of participants.^{27,30-33}

Such barriers, and possible strategies to circumvent them, have not been systematically reviewed within the last 6 years. The most recent systematic review concerning this topic was conducted in 2014, but the search was limited to studies on frail older adults.³³ A review from 2017³⁴ provided information about the effectiveness of strategies to

improve recruitment and retention of older individuals but did not report about barriers to recruitment or retention. Our systematic literature review summarizes frequently reported barriers and strategies that impact both recruitment and retention of older adults in clinical research to assist investigators in conducting research in the growing population of older people.

METHODS

This systematic literature review was conducted in compliance with the “PRISMA Statement” (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).³⁵ A PRISMA checklist is provided in the supplemental material section (Supplementary Data Set S1). A research protocol was preregistered with the open-access online platform Protocols.io.³⁶

Search Strategy

The online biomedical and life science databases MEDLINE (via PubMed), Embase (via Ovid), and the Cochrane Central Register of Controlled Trials (via Cochrane Library) were searched. Search strings were crafted with the PICOS (the Population being people aged 65 years or older, the Intervention being any, the Comparator being any, the Outcome being recruitment or retention strategies or barriers, and the Study design being any) method and adapted to the individual search algorithms of each database. The full search strategy has been described in the protocol (dx.doi.org/10.17504/protocols.io.4f6gtre).³⁶ Additionally, an extensive search by hand was performed as to not miss relevant

publications. All results were imported to a bibliographic management software (Endnote X7.8).

Eligibility

Publications were included that stemmed from original research that reported on barriers to or strategies for better recruitment or retention of older people (defined as being ≥ 65 years old) in clinical research. Only articles in English, German, French, or Spanish were included based on the language proficiency of the authors. Duplicate articles were removed.

Study Selection

The eligibility of each publication was determined independently by two authors (N.F. and A.P.), and a decision was made regarding its inclusion or exclusion. All articles were screened by title and abstract. Potentially eligible articles were assessed using the full text on procurement. Afterwards, consensus on study inclusion was achieved between the two reviewers via discussion and, if necessary, by consultation of a third reviewer (Y.P.).

Data Extraction

Microsoft Excel 2008 (Microsoft Corp) software was used for data extraction, management, and analysis. Data were extracted with predefined Excel sheets as follows: (1) first author and year of publication of the study; (2) sample size; (3) population characteristics; (4) factors impeding recruitment; (5) factors impeding retention; (6) factors improving recruitment; (7) factors improving retention; and (8) information on barriers or strategies concerning specific subgroups within the older population. For subgroup analyses, additional data were extracted ad hoc.

Quality Assessment and Risk of Bias

A quality assessment was not performed because efficacy or safety data were not analyzed. Furthermore, a variety of study types were included for which no single risk of bias assessment tool exists.

RESULTS

A database search, conducted on June 26, 2019, identified 1,281 articles, of which 50 were deemed eligible (see Figure 1 for a flow chart and Supplementary Data Set S2 for a list of all included studies). Information about the author, the year of publication, the country in which each study was conducted, the sample size, the required minimum age or age range, and the characteristics of the investigated participants is presented in Table 1.

Barriers Impeding the Recruitment of Older Adults into Clinical Trials

Factors described to have a negative impact on recruitment are shown in Figure 2. Study eligibility criteria that excluded potential participants due to comorbidities (46% of included trials), a decreased life expectancy (28%), and

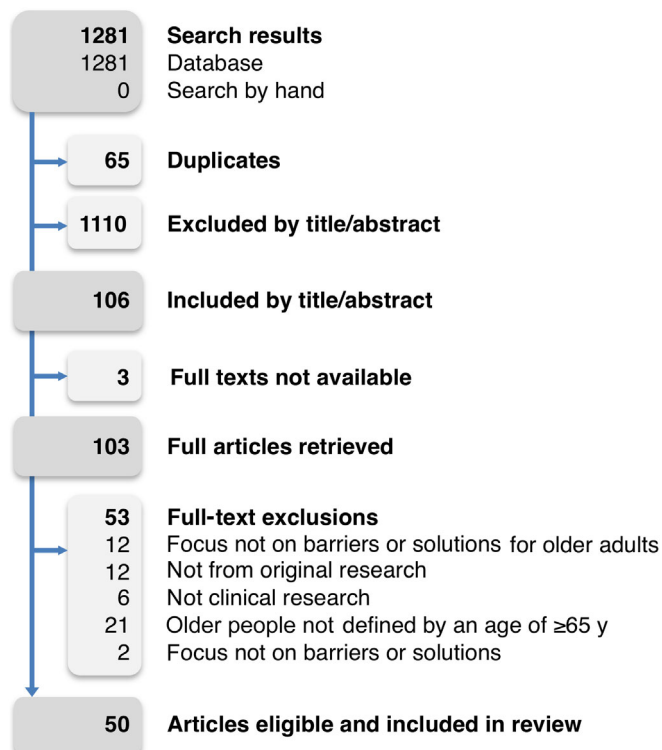


Figure 1. Article selection flowchart. [Color figure can be viewed at wileyonlinelibrary.com]

Table 1. Characteristics of Included Studies

First author	Year	Country	Sample size	Age, y ^a	Other criteria
Silagy	1991	AUS	400 ^b	≥70	No preexisting cardiovascular disease
Hirsch	1992	US	5,594 ^c	≥65	No terminal or dementing illness
Ives	1992	US	3,884 ^b	65–79	cl, rural
Anderson	1995	US	429 ^{b,c}	≥65	cl, diagnosis of diabetes mellitus
Slymen	1996	US	1,785 ^d	≥65	Sharp Rees-Stealy Medical Group
Adams	1997	US	442 ^b	≥65	cl, current health problems
Boles	2000	US	1,259 ^{b,c}	≥65	Healthy
Schmidt	2000	US	56 ^d	≥70	cl, limited mobility
Gill	2001	US	188 ^b	≥75	cl, frail, nondemented
Allsup	2002	UK	1,173 ^c	65–74	Fit, healthy
Bos	2002	NL	38 ^b	≥65	Healthy
Ory	2002	US	2,215 ^e	60–75	cl or living in nursing homes
Areán	2003	US	121 ^b	≥65	Depression, anxiety, drinking
Freret	2003	US	287 ^b	≥70	Transitioning into frailty
Gismondì	2005	US	1,103 ^{b,c}	≥65	cl, healthy
Gross	2005	US	36,167 ^f	≥65	Participants of 33 cancer trials
Ramsbottom	2006	UK	163 ^c	≥65	Admitted to hospital
Csipke	2006	UK	33 ^b	≥65	Depressed
Fitzpatrick	2006	US	10,036 ^{b,c}	≥75	CHS cohort members and others
Clemson	2007	AUS	310 ^b	≥70	cl, at risk of falling/previous fall
Gonzalez	2007	US	295 ^b	≥65	Healthy, racially diverse
Katula	2007	US	424 ^b	70–85	cl, increased risk for disability
Macias	2007	US	1,358 ^{b,c}	≥60	Veterans, new onset of seizures
Ross	2007	CAN	72 ^b	≥65	cl, female, overactive bladder
Zermansky	2007	UK	661 ^c	≥65	≥1 Medicine, living in care home
Basche	2008	US	300 ^c	≥65	Advanced tumors, received chemotherapy
Harris	2008	UK	833 ^{b,c}	≥65	cl, able to walk outside home
Peri	2008	NZL	1,444 ^{b,c}	≥65	Living in low-level dependency homes
Sanders	2009	AUS	2,317 ^b	≥70	Female, increased risk of falls or fractures
Forster	2010	UK	843 ^{b,c}	65–85	cl
Hinrichs	2013	DE	209 ^b	≥70	cl, chronically ill, mobility restricted
Kolanowski	2013	US	918 ^{b,c}	≥65	cl, before hospitalization, dementia/delirium
Marsh	2013	US	7,211 ^{b,c}	70–89	Sedentary, increased risk for mobility disability
McLean	2014	NZL	3,893 ^e	≥65	Ø
Michelet	2014	NOR	155 ^{b,c}	≥65	History of stroke or TIA, living in own home
Smorenburg	2014	NL	260,700 ^{b,c}	≥65	Healthy
Park	2015	US	84 ^b	≥65	cl, osteoarthritis
Piantadosi	2015	AUS	767 ^{b,c}	≥65	cl, undernourished
Samus	2015	US	1,275 ^{b,c}	≥70	cl, dementia or other cognitive disorder
Tamariz	2015	US	3,591 ^b	≥75	Hypertension
Apostolova	2017	DE	322 ^{b,c}	≥65	Hospitalized for acute illness
Gill	2018	US	31,872 ^{b,c}	≥70	cl, increased risk of serious fall injuries
Chatters	2018	UK	445 ^f	≥65	Ø
Duckham	2018	AUS	517 ^{b,c}	≥65	In retirement villages, increased falls risk
Nkimheng	2018	US	300 ^b	≥65	cl, functional difficulties
O'Hare	2018	AUS	708 ^{b,c}	≥70	Healthy
Plante	2018	US	123 ^b	≥70	Noninstitutionalized, low vitamin D
Ecarnot	2019	FR	16 ^c	≥65	Recent myocardial infarction
Lockery	2019	AUS, US	19,114 ^b	≥65	No history of cardiovascular disease
Viken	2019	NOR	1,514 ^b	70–76	Ø

Abbreviations: Ø, no details; AUS, Australia; CAN, Canada; cl, community living; CHS, Cardiovascular Health Study; DE, Germany; FR, France; NL, Netherlands; NOR, Norway; NZL, New Zealand; TIA, transient ischemic attack; UK, United Kingdom; US, United States.

^aIn case of diverging inclusion criteria within one study, only the lowest age limit equal to or above 65 years is presented (because results of trials or recruitment sites allowing for an age <65 years were not considered).

^bRandomized sample (investigation of recruitment methods, strategies, or characteristics of recruited participants).

^cSample comprised exclusions/ineligible individuals and refusers (barriers to participation were investigated).

^dSample comprised only dropouts.

^eSeveral recruitment sites.

^fMultiple trial populations investigated.

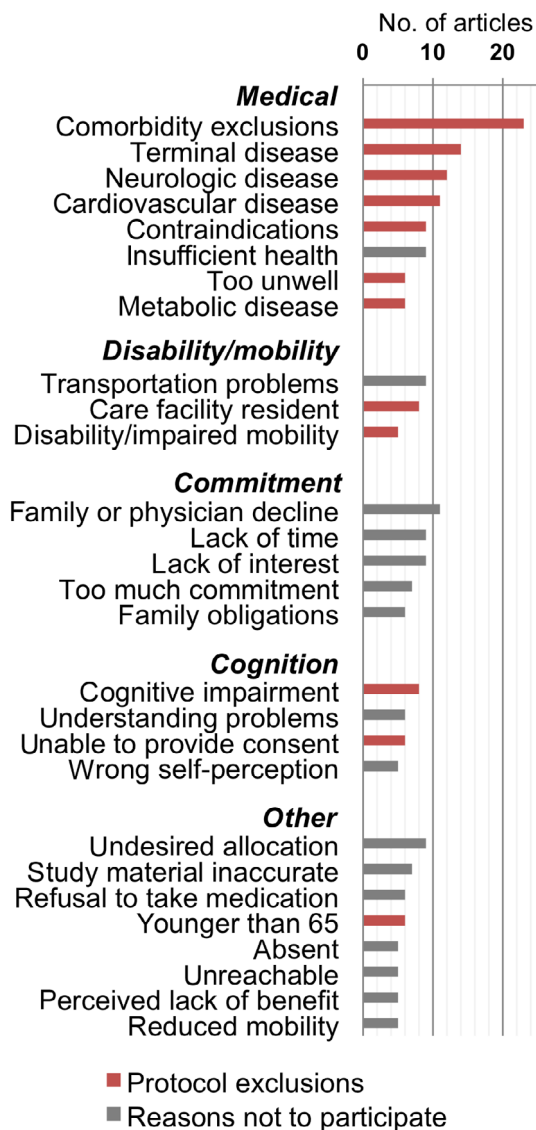


Figure 2. Barriers impeding the recruitment of older adults into clinical trials.

neurologic (24%) or cardiovascular diseases (22%) were the barriers most commonly reported to the inclusion of older people. Eleven studies (22%) reported that individuals declined participation in clinical trials on advice of their relatives or their general practitioner. Other reasons included lack of interest, the tendency to have lost interest during the recruitment process (18%), not feeling in sufficient health (18%), or having problems with transportation (18%). In a study on barriers to the participation of older patients in early-phase cancer clinical trials, data were gathered about specific reasons why transport was a problem: Primary concerns were to drive during bad weather (~71%), the amount of time needed to reach the study center (~66%), to drive after sunset (~53%), and the fear of not finding the center (~47%).³⁷ Other factors frequently mentioned included driving in the city or on the highway, worrying about parking, poor vision, and not being able to afford the travel to the clinic.³⁷ An analysis of the enrollment into cancer trials revealed that participants living closer to the

recruitment site tended to be older than participants who lived farther away.³⁸

In nine trials (18%), individuals did not want to risk being in the control group or taking the placebo because they were convinced about the intervention. Occasionally, they also dropped out after being assigned to the control group because they wanted to be in the active arm. The older individuals had time constraints (18%), they declined after realizing how much commitment was required (14%), perceived the study material as too complicated or long (14%), refused to take additional medication (12%), did not (fully) understand the study (12%), or had to care for a sick family member (12%).

Strategies to Recruit Higher Numbers of Older Adults into Clinical Trials

Investigators used a plethora of recruitment methods to reach out to older individuals. In Figure 3, methods with a positive effect on the recruitment of older adults are presented. Recruitment through letters and mailings yielded a satisfactory number of older participants, or successfully added older individuals to the study sample in 28% of the studies, whereas, in 4% of the included trials, it only resulted in few or no additional participants at all. Telephone calls following mailings increased the recruitment yield.^{39,40} Referrals from primary care providers⁴¹⁻⁴⁶ and geriatric assessment units⁴⁷ were reported to be effective for the recruitment of older adults (20%). Successful recruitment following newspaper advertisements was reported in more than half of all trials that relied on newspaper publicity to advertise their study (14%). The use of media, especially radio (14%), flyers (12%), and television (10%), was mostly ineffective to recruit older people (Figure 3).

To improve recruitment, 14 trials (28%) monitored their recruitment flow and made subsequent adaptations to their recruitment strategies. Before the start of one study, the recruitment methods were adapted according to lessons learned from a feasibility study that had been previously performed.⁴¹ Conducting recruitment at a convenient location (easy to reach or locality where the patient is anyway (e.g., own home or general practice)) was found important in 26% of the studies.

Provision of transport was considered to enhance recruitment (24%). Ten trials (20%) stressed the importance of effective support and minimization of additional work for people in charge of referrals and recruitment.

Seven studies (14%) reported that, before inclusion, their participants were informed about a payment ranging from “a small honorarium”⁴⁴ to payments above \$110.^{48,49} One study could only provide \$5 to their participants but, in the authors’ opinion, their participation rate would have been higher if the payment had been better.⁴⁴ Even though in one study incentives of about \$125 were paid and in another study gift certificates of \$50 were offered, the authors could not confirm that the payment had a significant impact on the willingness of individuals to participate.^{50,51} The potential recruits were more interested in quarterly examinations, team visits, and classes.⁵¹ People in whom the patients had confidence performed well as recruiters (12%), especially when they were experienced (12%), able to flexibly adapt to a patient’s schedule, and had an understanding for and genuine interest in older people (12%).

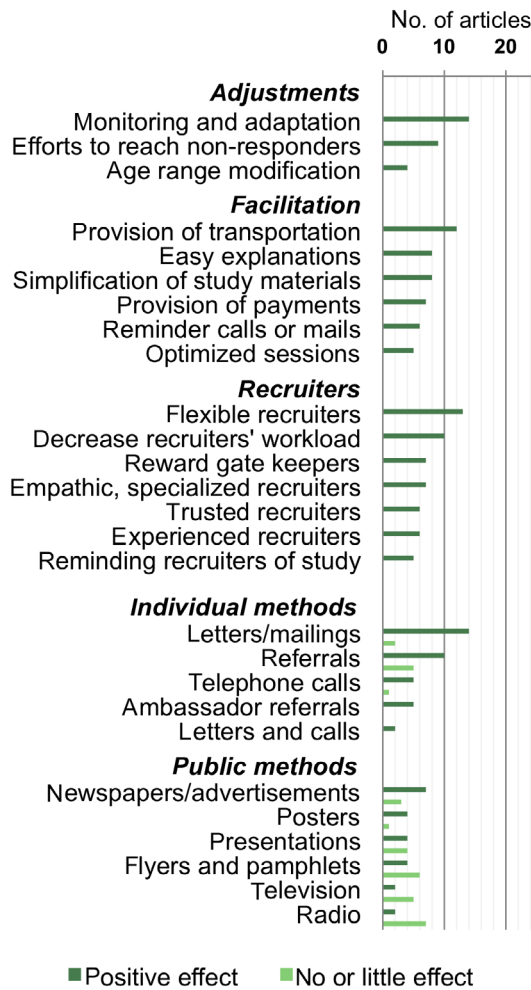


Figure 3. Strategies and methods to recruit higher numbers of older adults into clinical trials. [Color figure can be viewed at wileyonlinelibrary.com]

Barriers Impeding the Retention of Older Participants in Clinical Trials

The most common reasons reported for early termination of participation are listed in Figure 4. Most prevalent was death (12%), followed by withdrawal without giving an explanation (10%) and health problems (8%). However, sometimes the participants also lost interest in continuing with the study (6%).

Strategies to Retain Higher Numbers of Older Participants in Clinical Trials

Factors that positively affected the retention of older participants after inclusion into a trial are also presented in Figure 4. In 12% of the included trials, the research team regularly updated the participants about the study progress. Participants were offered a payment for continuation and completion (12%), a stable research staff was guaranteed (12%), and appreciation for participation was shown through small but thoughtful gestures (10%). Five studies (10%) mentioned that their participants were retained through researchers' flexibility concerning time and location of assessments.

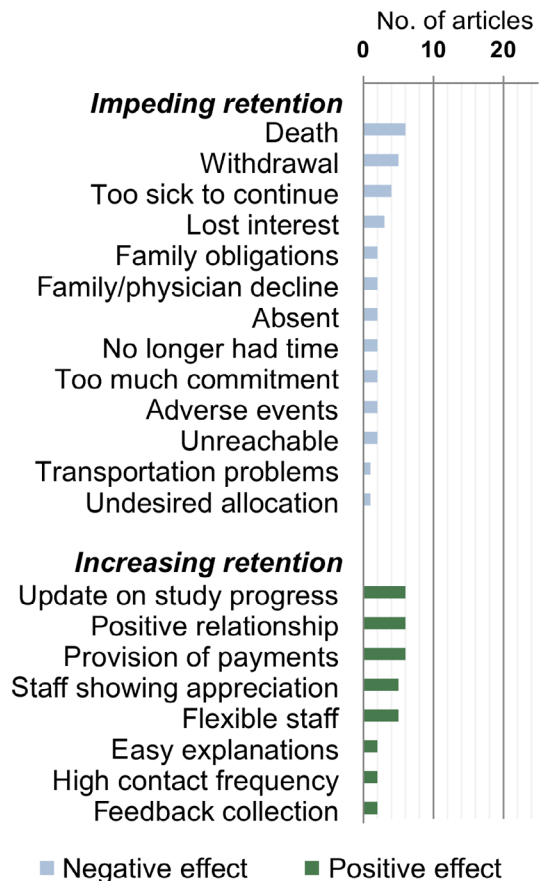


Figure 4. Factors improving or impeding the retention of older adults in clinical trials. [Color figure can be viewed at wileyonlinelibrary.com]

Minorities

Specific information on the recruitment and retention of older minorities, such as African American (also referred to as “Black”) and Hispanic (also referred to as “Latino” or “Spanish”) people, was provided by seven articles. A consumer-centered approach was used,^{41,52} and gate-keeper referral,^{41,52} face-to-face recruitment,⁴¹ mailings,⁴¹ and presentations to religious or ethnic groups⁴⁷ produced a high acceptance rate. Barriers in the recruitment of older minorities were mistrust,^{52,53} a heightened sense of cautiousness,⁵⁴ language barriers,^{52,53} difficulties to reach religious or ethnic groups,⁴⁷ higher incidences of comorbidities,⁵⁴ minority cultures not institutionalizing their older individuals,⁵³ and lack of documentation of race in clinical charts.⁵³ For successful recruitment, it was important to involve a trusted gatekeeper,⁵⁵ the potential participant’s family,⁵² to give clear information why the intervention is important,⁵² to develop culturally appropriate study materials,⁵⁶ to provide expansion of recruitment responsibilities to team members with affiliations to ethnic or religious groups,⁴⁷ and to provide involvement of community organizations.⁵⁵

For retention, monetary incentives⁵² and prescheduling the return visit⁵² were effective.

DISCUSSION

We successfully identified various barriers impeding the recruitment of older populations into clinical trials and found several strategies that can help researchers to include higher numbers of older individuals. We also found a few challenges and potential solutions concerning the retention of older people after being included in a study, but this information was rather sparse.

The most frequently cited barrier to the recruitment of older adults was related to exclusion criteria. Generic and specific comorbidities were the most prevalent exclusion criteria, with a negative impact on the inclusion of older adults in diabetes mellitus¹⁴ and heart failure¹⁶ trials, and were reported as common contraindications to participation in several other trials.⁵⁷⁻⁵⁹

Older patients were excluded due to short life expectancy in about 9% of reviewed studies (focusing on diabetes mellitus, type II).¹⁴ Nonpharmacological trials more often excluded potential participants with reduced life expectancy (~46%) than pharmacological trials (~21%).¹⁶ Exclusion criteria were often reported to be insufficiently justified or, more precisely, the protocol did not allow for a broader range of comorbidities that, even if present in the individual, would not lead to safety concerns.^{5,14,16} This result suggests that investigators should try to avoid rigid exclusion criteria instituted for safety reasons but rather focus on the actual individual health status of each potential participant. Where applicable, also a qualification period focused on optimization of health status (e.g., through adaptation of concomitant treatment) may help to include more older persons.

For most of the challenges that occur at the patient level, we could find potential solutions. Recruitment tracking allows researchers to adapt to applied methods and study procedures.⁶⁰

Consistent with our findings, a study investigating different recruitment methods through monitoring each method's success discovered that the use of newspapers that directly targeted the study's population produced the highest response and acceptance rates and was therefore an efficient and appropriate method to recruit older people.⁶⁰ Letters, mailings, and use of newspapers were adequate methods to recruit adults aged 65 years and older, whereas radio, flyers, and television proved ineffective. These results are contradictory to the results of a review performed in 2009 where mailings and referrals had little to no yield, but radio was successful in the recruitment of older adults.⁶¹ The authors of the review had abstracted data from articles published between 1978 and 2007. Therefore, the results may not necessarily be relevant to the situation in 2020. However, it can be assumed that through the development of alternative media, such as the internet, the importance of radio, newspaper, and other commonly used methods has decreased. In a study in 2018,⁶² recruitment of older than 60-year-old volunteers through social media (Facebook) surpassed traditional recruitment methods; and in 2014, efforts were made to develop and test a senior-friendly mobile interface prototype.⁶³ Using social media should certainly be considered in combination with several other recruitment methods⁶⁴ for future trials and may help to reach otherwise isolated older individuals. However,

potential dangers, such as misuse of personal data due to older people being uncritical or confused, must be taken into consideration.⁶⁵

Minority samples in our included studies were primarily African American and Hispanic populations. To involve these older ethnic minorities into clinical trials, contact with the community^{66,67} and consideration of special cultural vulnerabilities⁶⁶ were essential. In the literature, minority samples were composed of individuals stemming from different origins. Further in-depth research on specific factors and their influence on these individual groups and other subgroups within the older population concerning recruitment and retention into clinical trials is needed.

Investigators need to gain an understanding of older people's needs before the study, and recruiters should address concerns of the family of potential participants through their involvement during the recruitment process.^{21,32,61,68} Flexibility in scheduling with adaptation to older adults' preferences concerning time and place of assessment also seems to be important. Transport to the research site helped to overcome mobility issues and the problem of distance from research centers.²¹ The importance of this result was emphasized by a study investigating older adults' use of transportation, which resulted in a recommendation to consider the preferred mode of transportation of adults 65 years of age or older, as older drivers and public transport users were more likely to participate than those relying on adapted transport or taxi.⁶⁹

Regarding staff issues, workload for those responsible for referrals should be minimized through adequate support.^{32,70} A stable research staff also ensured familiarity and trust through close contact to the patient.^{32,33} Staff members should inform the participants regularly about changes and news concerning the trial to prevent loss of interest and subsequent withdrawal.^{21,32} For successful recruitment, engaging recruiters who are experienced in working with the older population^{21,32} and replacing their potentially existing prejudicial perceptions of aging individuals with adequate information through education⁷¹ are helpful.

Increasing the awareness of (new) staff members could be achieved through reminders and repeated explanations.⁶⁸ The staff should adapt time and place of appointments flexibly to fit the older adults' preferences³³ and should take a sufficient amount of time to explain study goals and procedures in simple language to let participants gain a full understanding of the trial.^{30,33,61}

With regard to retention, death, withdrawal without giving reasons, impaired health, and loss of interest were reasons given for early termination in the older population. A prior review supports this finding and reported that information about reasons for the discontinuation of older people in clinical studies was sparse.³³ Our low yield of results in this domain confirms their statement.

Social support was positively related to participants' satisfaction, and satisfaction resulted in a higher retention rate.⁷² Offering payment to the participants for continued participation and expression of appreciation had an increasing effect on the motivation and has been shown to keep the individual interested,^{21,70,73,74} even though two trials that were included in our review could not fully confirm this experience. One of the two trials was recruiting older

healthy volunteers for an invasive intervention. The participants were interested in science and had mainly altruistic motives to participate. The other study's participants were facility residents transitioning to frailty who prioritized health maintenance that was preserved through examinations, visits, and classes over monetary incentives. Therefore, it seems most older people felt rewarded, appreciated, and understood in their financial situation through payments offered for participation. Still, it is important to take into consideration that offering payments for participation tends to be more or less effective, depending on the individual older adult's living conditions and attitude toward the importance of research.

For high retention rates, we found it to be important to allow for flexibility to conduct the research assessments in a place closer to or inside the participant's home and at a time and date not conflicting with his or her schedule.²¹ In-person retention increased from approximately 37% to approximately 59% through offering home visits.⁷⁵

Careful analysis of potential dropout factors can improve sample size calculation. An accurate assessment of the proportion of dropouts allows for more generous recruitment goals to be set right from the start of the study and prevents loss of power or costly extensions. Conduction of feasibility studies also generates helpful insights for investigators about the suitability of their planned study design and about factors potentially impairing the study success that have not been previously anticipated. However, to identify factors influencing the retention of older people in clinical studies, and to quantify their impact, more research should be conducted in this field. A simple approach would be to analyze trials' follow-up flow charts, but a potential problem is that the information in these is usually coded in keywords and not detailed enough for in-depth comprehension.

Despite our efforts in maintaining a rigorous method, there are some limitations to our study. The articles included provided information from various continents with different healthcare systems as well as cultural and political aspects. Therefore, some of our results may not be applicable to every country in the world. Additionally, some of the articles are not necessarily current; the oldest was released almost 30 years ago, so the strength of the reported impact on the current population could be different. We quantified our results according to how many studies named a barrier or a solution and tried to bring together similar findings. However, some studies were small, whereas others included a large patient population. Thus, some factors that were cited by many studies were not necessarily those affecting the highest number of patients. Unfortunately, we consider the studies we found to be too heterogeneous in their reporting to allow for a formal meta-analysis with adequate weighting.

The main strength of our review is that the high number of studies that we yielded from searching three medical databases using a systematic literature search strategy is not limited to the English language. The search strategy and specified strict criteria concerning articles' eligibility for inclusion were prospectively published in a protocol. To increase the detection rate of relevant publications and to reduce the number of mistakenly excluded articles, two reviewers were involved in the study selection process. To

reduce the risk of systematic bias, they independently reviewed articles for eligibility, compared their decisions about inclusions afterwards, and consulted a third reviewer if their conclusions differed. We did not limit participants' characteristics to any particular health status and allowed for studies applying any type of intervention, so a heterogeneous sample of (potential) recruits was investigated that had a greater probability of accurately representing the actual older population.

We conclude that the study protocol should already be written with the manifold difficulties in mind that come with running a trial on the older population. Exclusion criteria need to be kept as liberal as possible, and recruitment methods should be constantly monitored and adjusted. We found several strategies that can improve recruitment and retention of older adults, but more research is needed to generate a more detailed and deeper understanding of the desires and preferences of older people concerning their (continued) participation in clinical studies.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Data Set S1: PRISMA checklist.

Supplementary Data Set S2: Included articles (1–50).