

Frailty in clinical drug trials: application to recruitment, subgroup analyses and outcomes

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Abstract

Clinical drug trials have traditionally focused on younger, healthier participants with less comorbidities and excluded frail older adults due to concerns regarding their ability to tolerate and respond to treatments. However, with population ageing, drug trials are increasingly turning their attention to older, frailer people. The aim of this review is to provide an overview of how frailty was assessed in published studies related to clinical pharmacological trials, and on the interaction of frailty on the safety and efficacy of the treatments. We searched MEDLINE, EMBASE and Cochrane for studies published in English that focused on clinical drug trials in older people. The review showed that frailty has been increasingly and successfully applied into clinical drug trials, especially trials in patients with cardiovascular disease and cancer. In most of the studies in the review, frailty was assessed retrospectively. How frailty was treated in statistical regression models was not consistent among the studies. Frailty was treated as an ordinal variable (with different levels of frailty) or binary variable (frail/non-frail) using cut-offs in some studies, and as a continuous in some other studies. There was heterogeneity in the effect of frailty, depending on the disease and treatment type. The results of this review suggest that frailty should not be assumed to always attenuate treatment effects, and routine measurement of frailty in participants in clinical drug trials would improve our knowledge of the effect of treatment in the frail and identify those who have more or least to gain from treatment.

Introduction

Clinical drug trials play a critical role in developing effective and safe therapeutic interventions and treatments. As the world's population ages, frailty is becoming an increasingly important, particularly in clinical practice and medical research. There is an urgent need to narrow the evidence practice gap in the treatment of older frail people. The projected global growth of older adults underwrites the need to have greater evidence on how to use medications safely and effectively in this vulnerable group. Although the interest in clinical trials involving frail older patients is increasing, there has been a large evidence gap for such people due to intended (and unintended) exclusion from clinical trials.^{1,2} Ageing and frailty are associated with many physiological changes such as increased body fat, reduced lean body mass and serum albumin, decreased liver function and reduced renal clearance.³ Older people, especially the frail, usually have increased sensitivity to many drugs due to changes in body compositions and organ functions that lead to altered drug absorption, distribution, metabolism and excretion.^{4,5} Frailty, defined as a state of increased vulnerability and reduced physiological reserve, carries an increased risk of poor outcomes in older adults.⁶ Clinical drug trials have traditionally focused on younger, healthier participants with less comorbidities who would be able to tolerate the medications and excluded frail older adults due to concerns regarding their ability to tolerate and respond to treatments. However, with the ageing population and a change in attitudes to older people (less ageism) frailty, , has become an increasing issue for drug trials. This has led to a growing recognition in recent years of the importance of including frail older adults in clinical drug trials. Over the past decades, increasing efforts have been made to include frailty assessment and to examine responses to drug effects according to baseline frailty in some randomised controlled trials.

The aim of this narrative review is to provide an overview of how frailty was assessed in published studies related to clinical pharmacological trials, and on the interaction of frailty on the safety and efficacy of the treatments.

Methods

We searched MEDLINE, EMBASE and Cochrane for studies published in English that focused on clinical drug trials in older people, using keywords “frailty”, “frail elderly”, “frail”, “pharmacology”, “clinical pharmacology”, “drug trial”. Abstracts were screened and any duplicates removed. We included randomised controlled drug trials that included older people and had included subgroup analyses by frailty.

Results

The search was conducted on 10th of April 2023, and after removing duplicates, 4031 abstracts were screened, 185 full texts were reviewed, and 18 relevant studies were included in this review (Figure 1). We have summarised the findings into four main clinical areas: cardiovascular; cognition; vaccination; cancer and other.

1. Cardiovascular drug trials

1.1. Blood pressure lowering

SPRINT: The Systolic Blood Pressure Intervention Trial (SPRINT) examined whether a lower systolic blood pressure (SBP) target of 120 mm Hg could reduce cardiovascular morbidity and mortality among hypertensive, nondiabetic adults.⁷ A total of 9361 participants with a SBP of 130 mm Hg or higher and an increased cardiovascular risk (but without diabetes) were randomly assigned to a SBP target of less than 120 mm Hg (intensive treatment) or SBP target of less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes. At 1 year, the mean SBP in the intensive-treatment group was lower compared to the standard-treatment group (121.4 mmHg versus 136.2 mm Hg, respectively). The intervention ceased early after a median follow-up of 3.26 years due to a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group: 1.65% per year vs. 2.19% per year, hazard ratio [HR] with intensive treatment 0.75 (95% confidence interval [CI] 0.64 to 0.89, $P < 0.001$). All-cause mortality was also significantly lower in the intensive-treatment group (HR 0.73, 95% CI 0.60 to 0.90, $P = 0.003$). Rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive-treatment group than in the standard-treatment group. The SPRINT study protocol included measures of functional status and frailty. However, neither frailty status nor gait speed was a prespecified subgroup in the trial protocol. Frailty was defined using a 36-item frailty index (FI) in 9306 SPRINT participants. Cut-offs used to classify participants were FI ≤ 0.10 (fit), $0.10 < \text{FI} \leq 0.21$ (less fit), or $\text{FI} > 0.21$ (frail).⁸ Overall, the prevalence of frailty was 30.9% (33.4% in the intervention group and 28.4% in the control group). In multivariable analyses, a 1% increase in the FI was associated with increased risk for self-reported falls (HR = 1.030), injurious falls (HR = 1.035), and all-cause hospitalizations (HR = 1.038) (all p values < 0.0001).⁸ In 2016, Williamson et al reported the results for the prespecified subgroup of SPRINT participants aged 75 years or older with hypertension. The authors concluded that among ambulatory adults aged 75 years or older, treating to an SBP target of less than 120 mm Hg compared with an SBP target of less than 140 mm Hg resulted in significantly lower rates of fatal and nonfatal major cardiovascular events and death from any cause. Exploratory secondary analyses were conducted to examine modification of the treatment effect by frailty status, and the investigators found that *frail participants exhibited smaller inter treatment group differences* (10.8 mm Hg) compared with less fit participants (11.3 mm Hg) and fit participants (13.5 mm Hg), with no significant difference in adverse events.⁹

HYVET: The Hypertension in the Very Elderly Trial (HYVET) study was a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over, and obtained frailty adjusted estimates of the effect of treatment with antihypertensive medication on risk of stroke, cardiovascular events,

and mortality. Participants in HYVET were randomised 1:1 to active treatment with indapamide sustained release 1.5 mg $\pm$ perindopril 2 to 4 mg or to matching placebo. The FI was calculated at entry, based on 60 potential deficits (minimum 30 deficits). The mean value of FI was 0.19 (standard deviation (SD), 0.10). Participants with an FI $\geq$ 0.10 were considered as the least frail, while those with FI $\geq$ 0.35 were considered the frailest. When examining the effect of frailty on treatment effect, estimated HRs for treatment effect were calculated for 6 FI categories: 0.1, 0.2, 0.3, 0.4, 0.5, 0.6. Cox regression analysis was used to assess the impact of FI at entry to the study on subsequent risk of stroke, total mortality, and cardiovascular events. Models were stratified by region of recruitment and adjusted for sex and age at entry. The investigators found that the point estimates of the HRs for the treatment effect decreased as FI increased, although to varying degrees and with varying certainty. The investigators found *no evidence of an interaction between effect of treatment for hypertension and frailty as measured by the FI. Both the frailer and the fitter older adults with hypertension appeared to gain from treatment*.

1.2. Heart failure treatment:

TOPCAT: The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial compared the use of spironolactone 15–45 mg daily with placebo in 3445 patients with symptomatic HFpEF from six countries. The primary study outcome was a composite of death from cardiovascular causes, aborted cardiac arrest or hospitalization for the management of heart failure. Secondary outcomes included cardiovascular death, heart failure hospitalization and all-cause mortality. Although the overall study result was neutral with regard to the primary endpoint, spironolactone was associated with a reduction in both cardiovascular death and heart failure hospitalization in a post-hoc analysis of subjects enrolled in the Americas.¹⁰ In 2018, Sanders and colleagues retrospectively constructed an FI using 39 clinical, laboratory, and self-reported variables in a subset of 1767 TOPCAT participants.¹¹ The mean FI at baseline was 0.37 $\pm$ 0.11. The cut-off to define frailty was FI $>$ 0.21. Overall, 94% of the participants were considered frail. When examining the impact of frailty on the study outcomes of cardiovascular death and heart failure hospitalization, the hazard ratios (HR) are represented per 0.10-point increase in FI (Group 1: FI $<$ 0.3 as the reference group; Group 2: FI 0.3–0.4; Group 3: FI 0.4–0.5; and Group 4: FI $\geq$ 0.5). The investigators found that greater frailty severity was associated with a higher risk of cardiovascular outcomes and mortality, however *the benefit of spironolactone on heart failure hospitalisation was not attenuated by frailty severity: HRs for heart failure hospitalisation 1.70 (95%CI 1.26-2.29) in Group 2, 2.11 (95%CI 1.55-2.86) in Group 3, and 4.12 (95%CI 3.01-5.66) in Group 4 (p value for interaction =0.35). A similar association was observed with all-cause mortality: HRs for all-cause mortality 1.32 (95%CI 1.00-1.73) in Group 2, 1.42 (95%CI 1.06-1.89) for Group 3, and 1.81 (95%CI 1.31-2.50) for Group 4.*¹¹

DAPA HF trial: The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial was a randomized, double blind, and placebo controlled to evaluate the efficacy and safety of sodium-glucose co-transporter 2 (SGLT2) inhibitors (10 mg of dapagliflozin once daily) compared with matching placebo, added to standard care in patients with heart failure and a reduced ejection fraction (HFrEF).¹² A total of 4744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less were randomly assigned to receive either dapagliflozin or placebo, in addition to recommended therapy, with a median follow up of 18.2 months. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death. The study found that among patients with HFrEF, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes.¹² In a post hoc analysis in 2022, the investigators retrospectively constructed a 32-item FI and examined the efficacy of dapagliflozin according to frailty status.¹³ A cut-off of FI $>$ 0.21 was also applied to define frailty, determining 49.6% of the participants as frail. However, frailty was treated as a categorical variable with three values in the regression models: FI class 1 (FI $\geq$ 0.210; not frail), FI class 2 (FI 0.211 to 0.310; more frail), and FI class 3 (FI $\geq$ 0.311; most frail). The authors found that

dapagliflozin improved all outcomes examined, regardless of frailty status, and the absolute reductions were

larger in frailer patients: HRs for the primary outcomes were 0.72 (95%CI 0.59-0.89) in participants with FI[?]0.21, 0.77 (95%CI 0.62 to 0.97) in the more frail group, and 0.71 (95%CI 0.54 to 0.93) in the most frail group.

DELIVER trial: The Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial aimed to examine whether SGLT2 inhibitors are effective in patients with heart failure with preserved ejection fraction (HFpEF). Participants (n=6263) were randomly assigned to receive dapagliflozin (at a dose of 10 mg once daily) or matching placebo, in addition to usual therapy. The primary outcome was a composite of worsening heart failure (which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death, as assessed in a time-to-event analysis. The investigators found that dapagliflozin, compared with placebo, reduced the risk of worsening HF events or cardiovascular death and improved symptoms in the participants.¹⁴ In a prespecified analysis published recently, the authors examined the efficacy and safety of dapagliflozin according to frailty status using the Rockwood cumulative deficit approach.¹⁵ A 30-item FI was created. Similar to the DAPA HF study, participants were divided into the following 3 subgroups: FI [?]0.210 (FI class 1, not frail); FI 0.211 to 0.310 (FI class 2, moderately frail); and FI [?]0.311 (FI class 3, most frail). The mean FI was 0.248 (SD 0.092). In total, 2354 (37.6%) patients were not frail (FI [?]0.210), 2413 (38.6%) were moderately frail (FI 0.211–0.310), and 1491 (23.8%) were in class 3 frailty (FI [?]0.311; ie, most frail). The analysis showed that *the benefit of dapagliflozin was consistent across the range of frailty studied*. For the primary composite outcome, compared with placebo, dapagliflozin reduced the risk of worsening HF or cardiovascular death across FI classes: the HRs from lowest to highest FI class were 0.85 (95% CI 0.68–1.06), 0.89 (95% CI 0.74–1.08), and 0.74 (95% CI 0.61–0.91), respectively (p for interaction = 0.40). The improvement in health-related quality of life with dapagliflozin occurred early and was greater in patients with a higher level of frailty: Although patients with a greater degree of frailty had worse Kansas City Cardiomyopathy Questionnaire scores at baseline, their improvement with dapagliflozin was greater compared to patients who were less frail: placebo-corrected improvement in Kansas City Cardiomyopathy Questionnaire Overall Summary Score at 4 months in FI class 1 was 0.3 (95% CI, -0.9 to 1.4); in class 2, 1.5 (0.3–2.7); and in class 3, 3.4 (1.7–5.1; p value for interaction = 0.021). The authors suggested that these findings should challenge any clinical reluctance to introduce dapagliflozin in patients perceived to be frail.

1.3. Antiplatelets

ASPREE: The Aspirin in Reducing Events in the Elderly (ASPREE) study was a primary prevention trial that investigated whether the daily use of 100 mg of enteric-coated aspirin would prolong the healthy life span of older adults.¹⁶ The trial recruited 19,114 participants, 9525 assigned to receive aspirin and 9589 to receive placebo. The primary end point was disability-free survival, which was defined as survival free from dementia or persistent physical disability. The primary composite end point was derived from the first end-point events of death, dementia, or persistent physical disability. The trial found that the use of low-dose aspirin did not differ significantly from placebo in influencing the rate of the primary end point after a median of 4.7 years of follow-up.

In an analysis on the effect of aspirin on all-cause mortality, the investigators found that ASPREE participants who received daily aspirin had higher all-cause mortality. The HR for all-cause mortality in the frail and non-frail were 1.36 (0.85-2.19) and 1.26 (95%CI 1.04-1.53) respectively.¹⁷ In this analysis, frailty was assessed at baseline using the adapted Fried frailty criteria, which included body weight, strength, exhaustion, walking speed, and physical activity.¹⁷

In a recent published paper in 2022, Ryan and colleagues aimed to adapt the deficit-accumulation FI approach to determine frailty status in ASPREE participants, to characterize the FI in terms of its association with age and physical health, and to compare it to the modified Fried's frailty phenotype. This study also aimed to validate the ASPREE FI by determining its predictive capacity for dementia-free survival and DFS and persistent physical disability over 5 years. The FI was constructed based on 67 items (n=19 110). The median FI score was 0.10 (interquartile range: 0.07–0.14) at baseline, and the cut-point to define frailty was FI > 0.21 (8.1% of the participants were defined as frail at baseline). Frailty was associated with the primary

composite outcome capturing independent life lived free of major disability and dementia, and increased the rate of persistent physical disability (HR 21.3, 95% CI 15.6–28.9). FI strongly associated with a modified Fried’s frailty phenotype ($p < .0001$, for all comparisons).¹⁸

1.4. Anticoagulants

The ELDERCARE-AF (Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients) trial aimed to compare the efficacy and safety of very-low-dose edoxaban (15mg) vs placebo in very elderly Japanese patients (aged 80 years or older) with AF who were considered ineligible for standard oral anticoagulant (OAC) therapy because of their high bleeding risk.¹⁹ The trial found that edoxaban 15 mg was effective at preventing stroke and systemic embolism (SSE) and did not significantly increase the incidence of major bleeding compared with placebo. In that trial, frailty was prospectively assessed using the Japanese version of the Fried’s frailty criteria. Approximately 40% were classified as frail (having a frailty score 3 or higher). Post hoc analysis aimed to compare very-low-dose edoxaban (15mg daily) vs placebo across frailty status among the ELDERCARE-AF participants. The primary efficacy end point was the composite of stroke or systemic embolism, and the primary safety end point was major bleeding. A total of 984 patients were randomly assigned to treatment (492 each to the edoxaban and placebo groups); 944 patients (402 frail patients [42.6%]; 542 non-frail patients [57.4%]; mean [SD] age, 86.6 [4.3] years; 541 women [57.3%]) were included in this analysis. The analysis showed that *regardless of frailty status, once-daily 15-mg edoxaban was associated with reduced incidence of stroke or systemic embolism* and may be a suitable treatment option for these patients.²⁰

1.5. Anti-diabetic therapies

ADVANCE trial: The Action in Diabetes and Vascular Disease - Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial was a 2 by 2 factorial design randomised controlled trial of 11,140 participants in 215 collaborating centres in 20 countries.^{21,22} The trial included two randomised interventions: (1) a double-blind assessment of the effects on vascular disease of a fixed combination of perindopril/indapamide vs placebo and (2) an open-label evaluation of an intensive glucose-lowering regimen (lowering the glycated haemoglobin value to a target of 6.5% or less) using modified release gliclazide vs standard care. In a post hoc analysis published in 2021, frailty was retrospectively assessed using a 34-item FI.²³ In this analysis, the mean FI was 0.17 (SD 0.08), and with the cut point of 0.21, the prevalence of frailty was 25.7% in the study participants. Frailty was treated as a binary variable (frail/ non-frail) in models examining the effect of frailty on the study outcomes. *The effect of intensive glucose treatment on primary outcomes showed some evidence of attenuation in the frail* : HRs for combined major macro- and micro-vascular events 1.03 (95% CI 0.90–1.19) in the frail versus 0.84 (95% CI 0.74–0.94) in the non-frail ($P = 0.02$). A similar trend was observed with blood pressure intervention. Severe hypoglycemia rates (per 1,000 person-years) were higher in the frail: 8.39 (6.15–10.63) vs. 4.80 (3.84–5.76) in non-frail ($P < 0.001$).

2. Trials aiming to improve cognitive function

MAPT: the Multidomain Alzheimer Preventive Trial (MAPT) trial tested the effect of omega 3 polyunsaturated fatty acid supplementation and a multidomain intervention (physical activity, cognitive training, and nutritional advice), alone or in combination, compared with placebo, on cognitive decline.²⁴ It was a 3-year, multicentre, randomised, placebo-controlled superiority trial with four parallel groups at 13 memory centres in France and Monaco. Participants were community-dwelling people aged 70 years or older without dementia, and had either relayed a spontaneous memory complaint to their physician, limitations in one instrumental activity of daily living, or slow gait speed. A total of 1680 participants were randomly assigned (1:1:1:1) to either the multidomain intervention (43 group sessions integrating cognitive training, physical activity, and nutrition, and three preventive consultations) plus omega 3 polyunsaturated fatty acids (ie, two capsules a day providing a total daily dose of 800 mg docosahexaenoic acid and 225 mg eicosapentaenoic acid), the multidomain intervention plus placebo, omega 3 polyunsaturated fatty acids alone, or placebo alone. The primary outcome was change from baseline to 36 months on a composite Z score combining four cognitive tests (free and total recall of the Free and Cued Selective Reminding test, ten Mini-Mental State

Examination orientation items, Digit Symbol Substitution Test, and Category Naming Test) in the modified intention-to-treat population. The study found that multidomain intervention and polyunsaturated fatty acids, either alone or in combination, had no significant effects on cognitive decline over 3 years in elderly people with memory complaints.

Secondary exploratory analysis from the MAPT²⁵ aimed to examine whether multidomain intervention and Omega-3 Polyunsaturated Fatty Acids supplementation can modify the cognitive function on elderly according to frail status. Frailty was defined by the adapted Fried's frailty phenotype, which included 5 components: (i) unintentional weight loss (self-reported unintentional loss of 4.5 kg or more recently); (ii) exhaustion (using two items of the Center for Epidemiologic Studies Depression Scale (16) (CES-D) : during the past week, "I felt that everything I did was an effort" and "I could not get going"); (iii) weakness (using the handgrip strength ascertained by dynamometer); (iv) slowness (the time needed to cover the four-meter walk) and (v) low energy expenditure (no engagement in physical activities). Participants meeting three or more criteria were classified as frail, those meeting one or two were considered prefrail, and those meeting none as non-frail. This analysis suggested that *the beneficial effect of multidomain intervention and n3 PUFA supplementation on cognitive function did not differ between frail and non-frail participants.*

3. Clinical trials related to vaccinations:

In an RCT published in 2009, Ridda and colleagues evaluated the immunogenicity of the 7-valent conjugated pneumococcal vaccine (PCV7) versus 23-valent polysaccharide vaccine (23vPPV) and compare the immune response to four serotypes (4, 6B, 18C and 19F), with respect to age or frailty in 241 patients aged 60 years who were previously unvaccinated hospitalized patients.²⁶ A 40-item FI were constructed prospectively to evaluate frailty in the participants. The presence of any item receives a score of one, and the total score is summed for each patient to give a Frailty Index measure. The minimum possible score is 0 (least frail) and the maximum is 40 (most frail). When examining immunological response at 6 months by frailty, the FI was treated as a binary variable, with a cut-off of 16. Frailty predicted poor immune responses to both polysaccharide and conjugate pneumococcal vaccines. Although there was some variation by serotype, responses after vaccination were lowest in the most frail or aged subjects.

In another double-blind, randomized, active-controlled, multicenter trial conducted by DiazGranados and colleagues,²⁷ participants aged [?]65 years were randomized 1:1 to receive a high-dose inactivated influenza vaccine (IIV-HD) or a standard-dose vaccine (IIV-SD) and followed for 6-8 months postvaccination for the occurrence of influenza. Frailty was prospectively measured. The study protocol prespecified several frailty-associated conditions based on deficit accumulation approach. At the time of enrolment, the study site collected the presence or absence of each of the following conditions, based on participant's self-report: vision loss, hearing loss, impaired mobility, difficulty toileting, difficulty bathing, difficulty dressing, difficulty grooming, difficulty going out, skin problems, resting tremor, changes in sleep, urinary complaints, gastrointestinal problems, and hypertension. When examining the impact of frailty on the efficacy of IIV-HD, frailty was treated as a categorical variable with 4 values: no frailty conditions, one frailty condition, two frailty conditions, and three or more frailty conditions. The study revealed that estimates of relative efficacy consistently favored IIV-HD over IIV-SD, and

there was no significant evidence that baseline age, comorbidity, or frailty modified the efficacy of IIV-HD relative to IIV-SD.

4. Drug trials in patients with cancer

The EMN01 study was designed to compare the progression-free survival (PFS) of elderly newly diagnosed multiple myeloma patients treated with triplet vs. doublet induction regimens and the PFS following maintenance treatment with lenalidomide-prednisone vs. lenalidomide alone. Before treatment, a geriatric assessment to assess patients' frailty status according to the International Myeloma Working Group (IMWG) Frailty Score was performed. In 2015, a frailty scoring system was developed by the (IMWG) that classifies patients into 3 frailty subgroups—fit, intermediate, and frail—based on age, comorbidities (Charlson comorbidity index, [?]1 vs. >1), Katz Activities of Daily Living (ADL) scale (>4 vs. [?]4), and Lawton

Instrumental Activities of Daily Living (IADL) scale (>5 vs. $[?]5$). Participants were stratified into 3 groups according to their frailty status: fit (total score 0), intermediate-fit (total score 1), and frail (total score ≥ 2). Post-hoc analysis according to frailty status in both induction and maintenance treatment arms showed that *fit patients benefit from a full-dose triplet regimen, while intermediate-fit and frail patients benefit from gentler regimens*. Frail patients had the highest rate of discontinuation due to adverse events; a trend towards a higher discontinuation due to adverse events was found in frail *vs.* fit patients.²⁸

The ALCYONE was a phase 3 trial in 706 patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation to receive nine cycles of bortezomib, melphalan, and prednisone either alone (control group) or with daratumumab (daratumumab group) until disease progression.²⁹ The primary end point was progression-free survival. In the primary analysis of the study (median follow-up 16.5 months), adding daratumumab to bortezomib/melphalan/prednisone (D-VMP) significantly prolonged progression-free survival over bortezomib/melphalan/prednisone (VMP) and induced deep responses in transplant-ineligible newly diagnosed multiple myeloma (NDMM) patients. After a median follow-up of 40.1 months, D-VMP continued to show significant progression-free survival benefit and significantly prolonged overall survival, even in patients aged $[?]75$ years.³⁰ In 2021, Mateos and colleagues conducted subgroup analysis of ALCYONE participants comparing D-VMP versus VMP by frailty status.³¹ Frailty scores were calculated retrospectively for all participants based on age ($[?]75$ years = 0 points; 76–80 years = 1 point, >80 years = 2 points), Charlson Comorbidity Index - CCI ($[?]1$ = 0 points; > 1 = 1 point), and the Eastern Cooperative Oncology Group performance status (ECOG PS) score (0 = 0 points; 1 = 1 point; $[?]2$ = 2 points). The sum of scores was used to classify patients as fit (0), intermediate (1), or frail ($[?]2$). When examining the impact of frailty on the intervention, frailty was treated as a binary variable: frail and non-frail. Those with a frailty status of fit (0) or intermediate (1) were collectively classified as non-frail. After a median follow-up of 40.1 months, the progression-free survival benefit of D-VMP versus VMP was maintained in all frailty subgroups: fit (HR 0.34, 95% CI 0.20-0.57), intermediate (HR 0.37, 95% CI 0.27-0.50), and frail (HR 0.51, 95% CI 0.39-0.68). *The study confirmed the clinical benefit of D-VMP in transplant-ineligible NDMM patients enrolled in ALCYONE, regardless of frailty status.*

Auner and colleagues examined the effect of age and frailty on the efficacy and tolerability of once-weekly selinexor, bortezomib, and dexamethasone in participants with previously treated multiple myeloma from the BOSTON trial.³² A recent FDA approval (December 18, 2020) was granted based on the phase 3 BOSTON trial in 402 patients with previously treated multiple myeloma, which demonstrated that the triplet combination of once-weekly selinexor with bortezomib and low dose dexamethasone (XVd) was superior to the standard twice-weekly combination of bortezomib and moderate dose dexamethasone (Vd). Among the 402 patients (195 on XVd, 207 on Vd) enrolled in the BOSTON study, 272 were non-frail (129 in the XVd arm and 143 in the Vd arm), 130 were considered frail with 66 in the XVd arm and 64 in the Vd arm. Frailty categories were assigned based on age, CCI, and ECOG PS. Frailty was treated as a binary variable: non-frail (0–1 points) or frail ($[?]2$ points). *The findings indicate that the combination of weekly selinexor with weekly bortezomib and dexamethasone was effective and safe in non-frail and frail patients*. Median progression-free survival was prolonged with XVd compared with Vd, with non-frail patients having a significantly longer progression-free survival (median 13.24 months) on XVd as compared to Vd (median 9.43 months) (HR 0.66, 95% CI 0.47–0.93), and frail patients showing a trend towards improvement on the triplet (XVd, median 13.93 months vs. Vd, 9.46 months; HR 0.69, 95% CI 0.40–1.17).

In the phase 3 MAIA study of patients with newly diagnosed multiple myeloma (NDMM) who were not eligible for transplant, daratumumab plus lenalidomide/dexamethasone (D-Rd) improved progression-free survival versus lenalidomide/dexamethasone (Rd).³³ Facon and colleagues conducted subgroup analysis of the MAIA study by frailty status.³⁴ Frailty assessment was performed retrospectively using age, Charlson comorbidity index, and baseline Eastern Cooperative Oncology Group performance status score. Frailty scores were used to classify patients into fit (0), intermediate (1), or frail ($[?]2$) subgroups. Of the randomized patients (D-Rd, $n = 368$; Rd, $n = 369$), 396 patients were non-frail (D-Rd, 196 [53.3%]; Rd, 200 [54.2%]) and 341 patients were frail (172 [46.7%]; 169 [45.8%]). The analysis showed that *the clinical benefit of D-Rd in transplant-ineligible NDMM patients enrolled in MAIA, regardless of frailty status.* After a 36.4-month

median follow-up, the progression-free survival benefit of D-Rd versus Rd was maintained across subgroups: HRs 0.41 (95% CI 0.22 - 0.75) in the fit group, 0.53 (95% CI 0.35 - 0.80) in the intermediate group, and 0.62 (95% CI 0.45 - 0.85) in the frail group.³⁴

5. Other drug trials

Rizka and colleagues aimed to determine the effect of alphacalcidol (a vitamin D analog) on inflammatory cytokines (IL-6, IL-10, g-IFN) and T cell subsets (CD4/CD8 ratio and CD8+ CD28-) of elderly people with various stages of frailty syndrome. This is a double blind RCT with allocation concealment, in 110 elderly participants, with an aim to examine the effect of 0.5 mcg alphacalcidol administration for 90 days on inflammatory cytokines (IL-6, IL-10, g-IFN) from PBMC culture supernatant, as well as CD4/CD8 and CD8+CD28- percentage using flow cytometry. Frailty was defined by Fried's frailty criteria and in the analysis, frailty was categorized into 3 groups: fit, prefrail and frail. The study revealed that alphacalcidol improves immune senescence by acting as anti-inflammatory agent through increased IL-10 and decreased IL6/IL-10 ratio and also improves cellular immunity through increased CD4/CD8 ratio and decreased CD8+ CD28- subset in elderly, and *the effect is not influenced by frailty state*.³⁵

In a recent published study, Hanlon and colleagues use individual-level participant data (IPD from industry-sponsored clinical trials for three exemplar chronic conditions (type 2 diabetes mellitus, rheumatoid arthritis, and chronic obstructive pulmonary disease) to construct a frailty index. The authors then examined the prevalence of frailty in these clinical trial populations and examine whether frailty is associated with serious adverse events in the clinical trials studied. The prevalence of frailty in these trials were 7–21% in type 2 diabetes mellitus trials, 33–73% in rheumatoid arthritis trials, and 15–22% in chronic obstructive pulmonary disease trials. Across all trials, and after adjusting for age, sex, and disease severity, *higher FI predicted increased risk of serious adverse events*; the pooled incidence rate ratios (per 0.1-point increase in FI scale) were 1.46 (95% CI 1.21–1.75), 1.45 (1.13–1.87), and 1.99 (1.43–2.76) for type 2 diabetes mellitus, rheumatoid arthritis, and chronic obstructive pulmonary disease, respectively.³⁶

Discussion and conclusion

The review showed that frailty has been increasingly and successfully applied into clinical drug trials, especially trials in patients with cardiovascular disease and cancer. In most of the studies in the review, frailty was assessed retrospectively. Only a few studies prospectively designed frailty assessment and subgroup analysis by frailty status.

There was heterogeneity in the effect of frailty, depending on the diseases and the treatment types. The effect of frailty on the treatment efficacy was not consistent among the studies in this review. While several trials like ADVANCE, SPRINT, ASPREE showed some reduced effects of the treatment in frail patients, most of the trials showed that the benefits of the treatment are not affected by frailty status. Some even showed that the benefits of the treatment were more significant in frailer patients (DAPA HF, DELIVER). There is a need to balance the benefits of medications with the risks of adverse effects. Frail patients are often perceived to be more vulnerable to the adverse effects of medications, and their poor health may make them more likely to experience adverse effects that could negatively impact the outcome of the trials. Additionally, frail patients are often taking multiple medications, which can increase the risk of drug interactions and further increase the risk of adverse effects. Our review suggests that frailty should not be assumed to attenuate the treatment effect, and it is important to include frailty assessment in future RCTs.

One of the most significant challenges of conducting frailty assessments in clinical drug trials is the lack of a standardized definition of frailty. There is currently no universally accepted definition of frailty, leading to confusion among researchers and a lack of comparability between studies. Moreover, frailty exists on a spectrum, and it can be difficult to determine at what point a patient is considered "frail." This lack of standardization makes it challenging for researchers to design clinical drug trials that include frail patients, as it is difficult to determine what criteria should be used to identify patients who are appropriate for inclusion in the study. This review raised a question on the best methods to evaluate frailty. The FI and Fried's frailty phenotype were applied in most of the trials in this review. The Frailty Index is one convenient method of

quantifying frailty and has excellent predictive value for adverse health outcomes in older people.^{37,38} The Frailty Index is based on the conceptualisation of frailty as an accumulation of deficits throughout life. It is constructed as the proportion of deficits present in an individual out of the total number of age-related health variables considered, with a value obtained from 0 to 1. This index can be established from almost any sets of health-related variables and is a feasible way to identify frailty in older hospitalised patients. The FI is good for baseline measurement in clinical trials. In the studies in this review, the deficit accumulation approach (FI) has been predominantly used compared to Fried’s frailty phenotype. On the other hand, Fried’s frailty phenotype may be more suitable if the investigators aim for repeated measurement of frailty from baseline to follow up and with an intention to improve frailty. The frailty phenotypic type may be changed based on the intervention targeted at frailty.

How frailty was treated in statistical regression models was not consistent among the studies. The FI was treated as an ordinal variable (with different levels of frailty) or binary variable (frail/non-frail) using cut-offs in some studies, and as a continuous in some other studies. The cut-point to define frailty was $FI > 0.21$ was consistently applied to define frailty in most of the studies. Similarly, with Fried’s frailty phenotype, some studies categorized participants into two groups of frail/non-frail, while other studies categorized participants into three groups of fit, prefrail and frail when conducting statistical analyses.

This review suggests that screening for frailty in participants in clinical drug trials would enable the identification of those that merit closer monitoring for adverse events. Trial data may be harnessed to inform disease management in people living with frailty. Overall, frailty has become an important consideration in clinical drug trials in older people. Including frail older adults in drug trials provides valuable information on the safety and efficacy of treatments, and allows researchers to examine the effect of drugs in different frailty subgroups. As such, frailty should continue to be used as a criterion for inclusion in clinical drug trials, to ensure that older adults of all frailty levels are appropriately represented in research. There may be significant challenges to conducting frailty assessments in clinical drug trials. Researchers must select appropriate assessment tools and overcome recruitment barriers to effectively assess frailty and ensure the success of clinical drug trials. The development of practical and efficient frailty assessment tools and increased efforts to recruit older adults with frailty can enhance the quality and relevance of clinical drug trials and improve the development of safe and effective treatments in older populations.

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Figure 1. The PRISMA flow diagram

