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# Frailty in older people: rehabilitation treatment research examining separate settings Plus (FORTRESS Plus): Results of a single-arm intervention study with comparison to historical controls

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## Abstract

# Background

Frail older adults hospitalised with acute illness are at high risk of functional decline, yet few receive intensive multidisciplinary rehabilitation during admission or after discharge. FORTRESS Plus was a single-arm study of a multicomponent frailty intervention comprising comprehensive geriatric assessment, pharmacy review, dietetic support, and up to seven weekly supervised home-based exercise sessions after discharge, compared with historical controls from the FORTRESS study, whose post-discharge support was limited to one to two home visits and weekly telephone calls.

# Methods

141 participants were recruited from three wards at Hornsby Ku-ring-gai Hospital, Sydney, Australia, between October 2023 and July 2024. The primary analysis compared 118 FORTRESS Plus participants meeting FORTRESS eligibility criteria (age ≥ 75, Mini Mental State Examination (MMSE) ≥ 24) with 110 FORTRESS historical controls. Health-related quality of life (EQ-5D-5L index and Visual Analogue Scale (VAS)) was assessed at baseline, 4 months, and 12 months. Secondary outcomes included physical function, mood, readmissions, social support, and medication burden.

# Results

Compared with historical controls, FORTRESS Plus participants had higher adjusted EQ-5D-5L index scores at 4 months (difference 0.22, 95% CI 0.12 to 0.32) and 12 months (difference 0.24, 95% CI 0.13 to 0.35; time-by-study interaction $p < 0.0001$ at both times). An average treatment effect of 0.17 (95% CI 0.01 to 0.34) was estimated after assigning an EQ-5D-5L index value of − 1 to participants who died before 12 months. Within FORTRESS Plus, physical function and mood improved: Short Physical Performance Battery (SPPB) scores increased by 1.71 points at 4 months and 2.47 points at 12 months, and Geriatric Depression Scale (GDS-15) scores decreased by 1.10 and 1.87 points, respectively (all $p < 0.05$). Readmissions did not differ significantly between studies.

# Conclusion

The more intensive multicomponent intervention in FORTRESS Plus was associated with a clinically meaningful improvement in health-related quality of life compared with the less intensive FORTRESS intervention. Physical function and mood also improved within FORTRESS Plus.

# Trial Registration

: The study was approved by the Northern Sydney Local Health District Human Research Ethics Committee (2023/ETH00649) and received site-specific governance approval (2023/STE01740). Trial registration: Australian New Zealand Clinical Trials Registry, ACTRN12623001103651, registered 20 October 2023.

# BACKGROUND

Frailty is a geriatric syndrome characterised by diminished physiological reserve and increased vulnerability to dependency, disability, risk of hospitalisation, institutionalisation, and mortality following exposure to stressors [1]. Frailty is common among older hospital inpatients, with around half classified as frail in one hospital-based study [2]. Frail older adults hospitalised with acute medical illness are at particular risk of new or additional disability, and only around 30% regain prior function in activities of daily living within one year of discharge [3]. Despite this, few frail older adults hospitalised with medical conditions (other than stroke or post-surgical conditions) receive intensive inpatient rehabilitation.

When rehabilitation services are provided, they are often short in duration and low in intensity, with limited support post-discharge [4]. These gaps in the assessment and management of frailty during hospitalisation and after discharge provided the rationale for developing the original FORTRESS intervention, which aimed to deliver more intensive, multicomponent rehabilitation across the hospital-to-home transition. The original FORTRESS study delivered an individualised, multicomponent frailty intervention combining additional inpatient physiotherapy, dietetic and pharmacy input with post-discharge community follow-up [5].

An audit of electronic medical records from some participants in the FORTRESS control group identified substantial evidence-practice gaps in usual care. Among the audited records, frailty assessment occurred in only 17% of admissions, progressive resistance training was delivered in 23%, nutritional intervention in 26%, and weight was recorded in 10% of admissions [4]. These findings, together with evidence linking low mood with frailty risk [6, 7], informed the design of FORTRESS Plus. The study strengthened post-discharge support, providing up to seven weekly supervised home-based exercise sessions, and additionally assessed mood as an outcome that had not been considered in the original FORTRESS study [5].

This paper reports the results of FORTRESS Plus, a single-arm intervention study with comparison to historical controls from the FORTRESS intervention arm [5]. The prespecified primary outcome was health-related quality of life, with secondary outcomes including physical function, mood, hospital readmissions, social support, and medication burden, as specified in the published trial protocol [8]. We evaluated whether the intervention provided in FORTRESS Plus was associated with greater improvement in health-related quality of life than the less intensive intervention received in the FORTRESS study, and described changes in physical function and depressive symptoms, as well as medication burden, social support, and hospital readmissions.

# METHODS

## Study design

FORTRESS Plus was a prospective single-arm intervention study evaluating an intensified multicomponent frailty intervention, compared with historical controls drawn from the intervention arm of the FORTRESS study. A historical-control design was adopted because the FORTRESS trial infrastructure, wards, screening procedures and outcome instruments were already in place, allowing evaluation of an intensified intervention without a new concurrent control group.

Three design features support comparability of the cohorts. First, both cohorts were recruited from the same three wards of the same hospital using the same FRAIL-scale screening procedure. Second, the comparative analysis is restricted to FORTRESS Plus participants meeting the original FORTRESS eligibility criteria (aged ≥ 75, MMSE ≥ 24), matching the historical controls on these criteria. Third, outcome assessment was identical: the same instruments administered on the same schedule, EQ-5D-5L utilities derived with the same Australian value set for both cohorts, and readmissions ascertained from the same electronic medical record system (EMR).

The principal differences between cohorts are calendar period (FORTRESS: September 2021 to December 2022; FORTRESS Plus: October 2023 to July 2024) and post-discharge intervention intensity. Recruitment of the historical cohort overlapped a period of COVID-19-related disruption to hospital services, which may have influenced admission thresholds, discharge pathways and hospital use. Because treatment allocation was not randomised, all comparative models prespecified adjustment for age, sex, baseline FRAIL score, baseline MMSE score and prior hospitalisation, with ward and participant as random effects, and a causal-inference analysis using augmented inverse probability weighting was performed as a secondary analysis. Residual confounding by unmeasured, time-varying factors cannot be excluded, and this is stated as the principal limitation of the study. This study is reported in accordance with the TREND (Transparent Reporting of Evaluations with Nonrandomized Designs) statement for the reporting of non-randomised evaluations of interventions [9]

## Recruitment

Participants for FORTRESS Plus were recruited from three acute hospital wards at Hornsby Ku-ring-gai Hospital, Sydney, Australia, between October 2023 and July 2024. Potentially eligible patients were identified through review of electronic medical records. A study nurse attended the participating wards and screened patients in person. Screening outcomes, eligibility status, and reasons for exclusion or non-enrolment were recorded in REDCap [10].

Eligible participants were community-dwelling adults aged 70 years or older who were hospitalised with an acute medical illness, had a FRAIL scale score of at least 3 at the time of entry into the study [11], a MMSE score of at least 22, and an expected survival of at least 12 months assessed using the Illness

Severity Rating. These criteria broadened those of the original FORTRESS study (aged 75 years or older, MMSE ≥ 24) to include adults aged 70 to 74 years and people with mild cognitive impairment, in response to the recruitment difficulties encountered during the FORTRESS study. All FORTRESS Plus participants were recruited under these broader criteria. For the comparative study, analyses were restricted to FORTRESS Plus participants who met the original FORTRESS eligibility criteria of 75 years or older and MMSE of at least 24, to match the criteria applied to the FORTRESS historical comparison group.

Cognitive function was assessed using the Standardised Mini-Mental State Examination (SMMSE) [12]. A license is not required for its use in Australia [13, 14]; the published guidelines are provided as an additional file in support. Participants required sufficient English to participate in the intervention. Patients were excluded if they were receiving palliative care, were not living in the community, or had experienced a new stroke during the recruitment hospitalisation.

The study used an approved opt-out recruitment process approved by the Northern Sydney Local Health District Ethics Committee. Patients received information about the study during their hospital admission and could opt out verbally or in writing. Participants who opted out continued to receive usual care on the participating wards, comprising routine geriatric medical care and allied health input as clinically indicated.

## The FORTRESS intervention

The FORTRESS study was a hybrid type II stepped wedge, cluster randomised trial conducted at the Hornsby-Ku-ring-gai Hospital, in which participants allocated to the intervention arm received an individualised multicomponent frailty intervention commencing during the acute admission. This included extra sessions of physiotherapy, dietetics, and pharmacy during the hospital stay, with an individualised Frailty Management Plan (FMP) developed from comprehensive geriatric assessment. The intervention continued in the community following discharge, consisting of one to two home visits plus four to six weekly telephone calls from a community implementation facilitator over four to six weeks, to support adherence to the recommendations made by hospital clinicians.

Much of the methodology and procedure developed for FORTRESS was carried over to FORTRESS Plus. Both studies used the same frailty screening with the FRAIL scale, cognitive assessment with the MMSE, recruitment from the same hospital wards, REDCap data capture, and the multicomponent intervention framework of comprehensive geriatric assessment with pharmacy and dietetic review and an individualised Frailty Management Plan. The principal difference was in the post-discharge phase, where the FORTRESS Plus exercise physiologist-delivered home-based exercise program replaced the facilitator home visits and telephone calls of FORTRESS, and in the broader eligibility criteria applied in FORTRESS Plus [8].

## The FORTRESS Plus intervention

FORTRESS Plus used an intensive extension of the original intervention. It included a comprehensive geriatric assessment, pharmacy review, an individualised Frailty Management Plan, targeted dietetic intervention where indicated, and up to seven weekly supervised home visits from an Exercise Physiologist.

The intervention comprised hospital and community phases. During the acute admission, participants received a comprehensive geriatric assessment, pharmacy review, and development of an individualised Frailty Management Plan. Pharmacy review included medication reconciliation, identification of polypharmacy, and deprescribing recommendations where clinically appropriate. Medication-related risk was assessed using the Drug Burden Index (DBI), calculated by the study pharmacist using the DBI Calculator embedded within the Goal-directed Medication review Electronic Decision Support System (G-MEDSS) [14].

Participants with unintentional weight loss of at least 5 kg or at least 5% of body weight during the preceding 12 months received dietetic assessment and nutritional intervention where indicated. This could include nutritional education, dietary goals, a high-protein, high-energy diet, and protein supplementation.

Following discharge, participants were offered up to seven weekly supervised home visits from an exercise physiologist. Visits commenced within one week of discharge where possible and lasted approximately 30 to 60 minutes. The exercise programme comprised progressive resistance and static and dynamic balance exercises adapted from the Otago Exercise Programme [15]. Participants were encouraged to exercise between supervised visits and to attend suitable community-based exercise programmes.

The Exercise Physiologist used motivational interviewing to establish participant-nominated SMART goals. Available social and family support was assessed and documented but did not constitute a separate treatment component or modify delivery of the intervention. Exercise adherence was assessed using participant-maintained exercise logs and Exercise Physiologist records of supervised sessions.

The 15 item Geriatric Depression Scale (GDS-15) [16] was not used to tailor the exercise, dietary, or medication components of FORTRESS Plus. However, participants with a GDS-15 score of at least 5 and clinical symptoms suggestive of depression were referred to the hospital Chronic Care Team geriatrician for further assessment. This referral pathway was separate from the core intervention components.

## Blinding

Blinding was not used. Participants and intervention providers were aware of intervention exposure. Outcome assessors were not blinded to intervention exposure because the Exercise Physiologist

delivered the post-discharge intervention and conducted the follow-up assessments. Historical hospital admission data abstractors were blinded to the study hypotheses and cohort status.

# Sample size

The planned sample size was 106 participants meeting the original FORTRESS eligibility criteria. This calculation was based on 80% power, a two-sided alpha level of 0.05, and the ability to detect a standardised between-cohort difference of 0.5 in the primary health-related quality-of-life outcome. A total of 141 participants were recruited, exceeding this target. The FORTRESS eligibility criteria (aged 75 years or older, MMSE at least 24) were broadened for FORTRESS Plus to include adults aged 70 to 74 years and those with mild cognitive impairment MMSE ≥ 22/30, with the aim of enhancing feasibility and participant engagement. In total 118 participants met the age and MMSE criteria for the comparative study. The remaining 23 participants were recruited under these broader eligibility criteria.

## Outcomes and assessments

The timing of outcome assessments is summarised in Table 1. The primary outcome was health-related quality of life, measured using the EQ-5D-5L index score at baseline, 4 months, and 12 months. EQ-5D-5L health-state profiles were converted to utility index scores using the Australian EQ-5D-5L value set developed by Norman et al. (2023) and its corresponding scoring algorithm [17]. The same value set and scoring procedures were applied to self-completed and proxy-completed questionnaires and to both cohorts. EQ-5D-5L index scores range from values below zero to 1, with higher scores indicating better health-related quality of life. In the development of the index, the value − 1 was taken to represent death. The EQ-5D Visual Analogue Scale (VAS) was analysed as a secondary measure and recorded on a 0 to 100 scale, with higher scores indicating better self-rated health. Baseline EQ-5D-5L and VAS assessments were completed during the hospital admission. Follow-up EQ-5D-5L and VAS assessments were completed at 4 and 12 months, either self-completed or proxy-completed as at baseline, during home visits or by telephone with the Exercise Physiologist, who administered the assessment but did not influence participant responses.

Table 1
Outcomes and assessment timepoints in FORTRESS Plus

| Outcome | Index admission | First home visit | 4 months | 12 months | Follow-up period |
|---|---|---|---|---|---|
| FRAIL Scale | X | | X | X | |
| EQ-5D-5L (index and VAS) | X | | X | X | |
| SPPB | | X | X | X | |
| GDS-15 | | X | X | X | |
| Drug Burden Index | X | | | X | |
| Weight | X | X | X | X | |
| Social support, carer involvement, motivational interviewing | | X | | | |
| Hospital readmissions (EMR) | | | | | X* |
| Adverse events | | | | | X |

**Any non-elective readmission during the 12 months post-recruitment, extracted from electronic medical records (EMR) after the 12-month assessment.*

*EQ-5D-5L: EuroQol 5-Dimension, 5-Level questionnaire; VAS: visual analogue scale; SPPB: Short Physical Performance Battery; GDS-15: 15-item Geriatric Depression Scale; DBI: Drug Burden Index; EMR: electronic medical record.*

Secondary outcomes were physical function, depressive symptoms, hospital readmissions, social support, and medication burden. Physical function was assessed using the Short Physical Performance Battery (SPPB) [18], with the total score calculated from the balance, gait-speed, and chair-stand components. Scores range from 0 to 12, with higher scores indicating better physical function. SPPB assessments were conducted at the first home visit and repeated at 4 and 12 months. Depressive symptoms were assessed using the 15-item Geriatric Depression Scale (GDS-15), with higher scores indicating more depressive symptoms [16]. GDS-15 assessments were conducted at the first home visit and repeated at 4 and 12 months.

The five-item FRAIL scale was completed during the hospital admission to determine eligibility and was included as a baseline covariate in analyses. FRAIL score was not assessed as a longitudinal outcome. It was, however, collected at both the 4 month and 12-month assessment. Medication burden was assessed using the Drug Burden Index (DBI), calculated by the study pharmacist using the Drug Burden Index Calculator embedded within the Goal-directed Medication review Electronic Decision Support System (G-MEDSS) [14]. DBI was assessed at baseline and 12 months and was not collected at the 4-month assessment.

Hospital readmissions were obtained from electronic medical records and included the number of non-elective readmissions and time to first readmission within 365 days of the index admission. Prior hospitalisation, which was included as a covariate, was defined as at least one hospitalisation involving an overnight stay during the 12 months preceding the index admission and was also obtained from electronic medical records.

Social support was assessed during home visits using participant self-report of available carer, family, or formal support and a rating of perceived support. Social support was assessed as an outcome and was not used to guide or modify intervention delivery. Because this was not a validated measure of social isolation, the outcome was referred to as social support rather than social isolation. Responses on perceived support used six ordered categories (very supportive, quite supportive, somewhat supportive, not very supportive, not at all supportive, and having no significant other).

Adverse events, serious adverse events, deaths, and withdrawals were recorded during the index hospital admission and throughout the intervention and follow-up periods. Deaths were recorded separately from other adverse events, including the timing of death and whether death occurred during the index admission or after discharge.

[Insert Table 1 here]

# Statistical analysis

All statistical analyses followed the intention to treat principle and were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Descriptive statistics were used to summarise participant characteristics, outcome distributions and participant follow-up. Continuous variables were summarised using means and standard deviations for approximately symmetric distributions, and medians and interquartile ranges for skewed distributions, based on inspection of the observed data distributions. Categorical variables were summarised using frequencies and percentages.

For analyses within the FORTRESS Plus intervention study only, changes in continuous health-related quality of life outcomes over time were estimated using mixed-effects models adjusted for ward, age, sex, baseline FRAIL score, baseline MMSE score, and hospitalisation during the preceding 12 months. Repeated observations from the same participant were accounted for using participant-level random effects.

For the comparative analyses of health-related quality of life (EQ-5D-5L index and VAS) between FORTRESS Plus and FORTRESS historical controls, mixed-effects models included fixed effects for time, study group, age, sex, baseline FRAIL score, baseline MMSE score, and hospitalisation during the preceding 12 months, together with the time-by-study interaction. Ward and participant status were included as random effects. Mean differences in health-related quality of life outcomes over time and changes over time were both examined and compared between studies. The primary comparison

determined whether changes in EQ-5D index over time differed between the two studies over 12 months, using the time-by-study interaction in the mixed-effects model.

Mixed-effects models handle missing follow-up via a missingness-at-random assumption. A secondary analysis was performed for EQ-5D index at 12 months using causal inference methodology for non-randomised data using the SAS causaltrt procedure and the augmented inverse probability weighting method to balance key prognostic factors including baseline EQ-5D-5L index, baseline FRAIL score, baseline MMSE score, age, sex, hospitalisation during the preceding 12 months, and ward. Estimates for the 'Average Treatment Effect' (ATE) were derived before and after multiple imputation of missing follow-up data, and additionally after assigning a value of − 1, the conventional lower bound representing the worst conceivable health state on the EQ-5D utility scale, to participants who died before 12-month follow-up. This conservative choice avoids potential bias introduced by treating deaths as a missing data problem.

Level of perceived social support was examined after mapping raw responses to a scale from 0 to 4, where 0 = no significant other or a relationship that was not at all supportive, 1 = little support (not very supportive), 2 = somewhat supportive, 3 = quite supportive, and 4 = very supportive. Participants generally provided responses on multiple home visits during the first 4 months, therefore an average value across all responses provided was calculated for further analysis.

Readmissions were obtained from electronic medical records and were restricted to non-elective events occurring within 365 days of the index admission. Time to first readmission and the composite outcome of readmission or death were analysed using Cox proportional-hazards models. Time to readmission was also examined in competing risk models, where death before readmission was treated as a competing event, with sub distribution and cause-specific hazard ratios estimated. Relative risks for any readmission within 365 days of index admission were estimated using modified Poisson regression. Adjusted time-to-event models and relative risks accounted for age, sex, hospitalisation during the preceding 12 months, baseline FRAIL score, and baseline MMSE score. The number of readmissions and total nights in hospital occurring within 12 months of index admission were compared using Kruskal-Wallis tests.

## RESULTS

# Participant flow and baseline characteristics

A total of 141 participants were recruited to FORTRESS Plus. Of these, 118 participants met the original FORTRESS eligibility criteria of age 75 years or older and MMSE score of at least 24 and were included in the comparative analyses with 110 historical controls from the FORTRESS intervention arm.

Follow-up data were available for 79 participants at 4 months and 60 participants at 12 months in the full FORTRESS Plus study. In the comparative study, follow-up data were available for 64 participants at 4 months and 48 participants at 12 months.

As FORTRESS Plus was not randomised, baseline characteristics of the two cohorts were compared descriptively (Table 2). The cohorts were broadly comparable in age, sex, and baseline cognitive status. FORTRESS Plus participants had a somewhat milder frailty profile than FORTRESS historical controls, and a higher proportion had been hospitalised in the preceding 12 months (57 of 118, 48.3%, vs 38 of 110, 34.5%). Given these differences and the non-randomised design involving historical controls, all comparative models adjusted for age, sex, baseline FRAIL score, baseline MMSE score, and hospitalisation in the preceding 12 months, with ward and participant as random effects

*MMSE, Mini-Mental State Examination; RACF, residential aged care facility. The comparative study cohort comprises FORTRESS Plus participants who met the original FORTRESS eligibility criteria (age ≥ 75 years, MMSE ≥ 24), analysed against 110 historical controls from the FORTRESS intervention arm*

Table 2
Baseline characteristics of FORTRESS Plus participants and historical FORTRESS participants

| **Variable** | **All FORTRESS Plus, *n* = 141** | **FORTRESS Plus, comparative study, *n* = 118** | **FORTRESS historical controls, *n* = 110** |
|---|---|---|---|
| Age, mean ± SD | 84.30 ± 6.68 | 85.67 ± 5.42 | 84.99 ± 5.36 |
| Female sex, n (%) | 78 (55.3%) | 68 (57.6%) | 61 (55.5%) |
| MMSE, mean ± SD | 26.10 ± 2.11 | 26.28 ± 1.82 | 26.88 ± 1.64 |
| FRAIL score 3 / 4 / 5, n (%) | 111 (78.7%) / 28 (19.9%) / 2 (1.4%) | 93 (78.8%) / 23 (19.5%) / 2 (1.7%) | 66 (60.0%) / 42 (38.2%) / 2 (1.8%) |
| Ward 2D / 3D / 4D, n (%) | 75 (53.2%) / 24 (17.0%) / 42 (29.8%) | 69 (58.5%) / 20 (16.9%) / 29 (24.6%) | 79 (71.8%), 23 (20.9%), 8 (7.3%) |
| Prior hospitalisation in preceding 12 months, *n* (%) | 73 (51.8%) | 57 (48.3%) | 38 (34.5%) |
| Baseline EQ-5D-5L index, mean ± SD | 0.48 ± 0.23 | 0.49 ± 0.22 | 0.53 ± 0.34 |
| Baseline EQ-5D VAS, mean ± SD | 58.58 ± 17.39 | 59.49 ± 16.99 | 55.05 ± 21.37 |

*EQ-5D-5L, EuroQol five-dimension five-level questionnaire; MMSE, Mini-Mental State Examination; SD, standard deviation; VAS, visual analogue scale.*

# Intervention exposure, adherence, and safety

Among the 141 enrolled participants, 140 (99.3%) received a pharmacy review during the index admission, 62 (44.0%) were referred to the ward dietitian for nutritional assessment, and comprehensive geriatric assessment was completed for 127 (90.1%). Polypharmacy, defined as regular use of five or

more medications, was identified in 135 participants (95.7%), and deprescribing or medication-review recommendations were made for 77 of these (57.0%).

Of 84 participants who received the intervention, participants attended a median of 7 supervised home visits (IQR 5–7; mean 5.9), and 54 (64.3%) completed all seven planned sessions. Exercise adherence, based on participant-maintained exercise logs and Exercise Physiologist records, averaged 4.9 self-reported sessions per week, with 62 of 84 (73.8%) rated as very or quite adherent by the treating Exercise Physiologist. Thirty-one of 84 participants (36.9%) participated in a community-based exercise programme during the intervention period. Sustained engagement was high: 58 of 79 participants assessed at 4 months (73.4%) were still engaging in the exercise programme, decreasing to 41 of 60 (67.2%) at 12 months.

Twenty deaths occurred during the study period: 4 during the index hospital admission and 16 during post-discharge follow-up. Falls and re-hospitalisations were documented in visit records. None of these events, including the deaths, were judged by the study team to be related to the intervention, and no other serious adverse events were recorded.

# Comparative analyses: FORTRESS Plus (n = 118) compared with FORTRESS historical controls (n = 110)

# Health-related quality of life

EQ-5D index increased over time in the FORTRESS Plus study but not overall in FORTRESS historical controls, both at 4 months and 12 months. Time by study interactions were significant overall, and at both 4 and 12 months (all $p < 0.0001$). The adjusted between-group difference in EQ-5D-5L index between FORTRESS Plus and FORTRESS was 0.22 at 4 months (95% CI 0.12 to 0.32) and 0.24 at 12 months (95% CI 0.13 to 0.35). The adjusted change from baseline to 4 months was − 0.03 (95% CI -0.10 to 0.05) in FORTRESS historical controls and 0.23 in FORTRESS Plus (95% CI 0.14 to 0.31). The adjusted change from baseline to 12 months was 0.01 (95% CI -0.07 to 0.09) and 0.28 (95% CI 0.19 to 0.37), respectively.

Table 3
Adjusted means and between-group differences for FORTRESS Plus versus FORTRESS historical controls in EQ-5D-5L index scores over time

| Time point | FORTRESS, adjusted mean (95% CI) | FORTRESS Plus, adjusted mean (95% CI) | Between-group difference for FORTRESS Plus vs FORTRESS (95% CI) |
|---|---|---|---|
| Baseline | 0.53 (0.47 to 0.59) | 0.50 (0.44 to 0.55) | −0.03 (− 0.12 to 0.05) |
| 4 months | 0.50 (0.43 to 0.57) | 0.72 (0.65 to 0.80) | 0.22 (0.12 to 0.32) |
| 12 months | 0.54 (0.47 to 0.61) | 0.78 (0.69 to 0.86) | 0.24 (0.13 to 0.35) |

*The comparative longitudinal mixed model included fixed effects for time, study group, age, sex, baseline FRAIL score, baseline MMSE score, and hospitalisation during the preceding 12 months, together with the time-by-study interaction. Ward and participant status were included as random effects.*

Estimates of average treatment effect using causal inference methodology are shown in Table 4. The secondary analysis of EQ-5D index outcomes at 12 months using inverse probability weighting supports the findings from the primary analysis, showing that EQ-5D was significantly higher at 12 months in FORTRESS Plus than in FORTRESS, after accounting for baseline EQ-5D-5L index, baseline FRAIL score, baseline MMSE score, age, sex, prior hospitalisation, and ward (ATE estimate 0.23 (95% CI 0.13 to 0.33, $p < 0.0001$) in multiply imputed data and 0.17 (95% CI 0.01 to 0.34, $p = .03$) after additionally assigning EQ-5D of − 1 in case of death).

Table 4
Estimates for 'Average Treatment Effect' (ATE) for FORTRESS PLUS versus FORTRESS historical controls in EQ-5D-5L index at 12 months, using causal inference analysis of non-randomised data with augmented inverse probability weighting

| **EQ-5D index** | **ATE estimate in available data only (95% CI), p value** | **ATE estimate in multiply imputed data (95% CI), p value** |
|---|---|---|
| | **0.28 (0.19 to 0.38), p < 0.0001** | **0.23 (0.13 to 0.33), p < 0.0001** |
| EQ-5D index extended with − 1 for deaths | | 0.17 (0.01 to 0.34), p = .03 |

*ATE is 'Average Treatment Effect' from causal inference for non-randomised data. Estimates accounted for baseline EQ-5D-5L index, baseline FRAIL score, baseline MMSE score, age, sex, prior hospitalisation, and ward.*

The overall time-by-study interaction for EQ-5D VAS scores was statistically significant ($p = 0.049$), indicating that EQ-5D VAS scores increased more over time from baseline in FORTRESS Plus than in FORTRESS historical controls. The baseline-to-4-month interaction was statistically significant ($p = 0.029$), whereas the baseline-to-12-month interaction was not statistically significant ($p = 0.061$).

The adjusted between-group difference in EQ-5D VAS score between FORTRESS Plus and FORTRESS was 5.3 at baseline (95% CI 0.2 to 10.6), 13.4 points at 4 months (95% CI 7.0 to 19.8) and 12.7 points at 12 months (95% CI 5.7 to 19.7). The adjusted change from baseline to 4 months was 1.3 points (95% CI − 3.7 to 6.2) in FORTRESS historical controls and 9.4 points (95% CI 4.0 to 14.8) in FORTRESS Plus. The corresponding changes to 12 months were 5.3 (95% CI 0.1 to 10.4) and 12.7 points (95% CI 6.8 to18.7), respectively.

Table 5
Adjusted means and between-group differences for FORTRESS Plus versus FORTRESS historical controls in EQ-5D VAS scores over time

| Time point | FORTRESS, adjusted mean (95% CI) | FORTRESS Plus, adjusted mean (95% CI) | Between-group difference for FORTRESS Plus vs FORTRESS (95% CI) |
|---|---|---|---|
| Baseline | 54.6 (50.9 to 58.3) | 59.9 (56.3 to 63.5) | 5.3 (0.2 to 10.6) |
| 4 months | 55.9 (51.8 to 60.0) | 69.3 (64.5 to 74.0) | 13.4 (7.0 to 19.8) |
| 12 months | 59.9 (55.5 to 64.2) | 72.6 (67.2 to 78.0) | 12.7 (5.7 to 19.7) |

*The comparative longitudinal mixed model included fixed effects for time, study group, age, sex, baseline FRAIL score, baseline MMSE score, and hospitalisation during the preceding 12 months, together with the time-by-study interaction. Ward and participant were included as random effects.*

# Hospital readmissions

Within 365 days of the index admission, 66 of 118 FORTRESS Plus participants (56%) and 56 of 110 FORTRESS historical controls (51%) experienced a non-elective readmission. Death before any recorded readmission occurred in four FORTRESS Plus participants (3%) and 10 FORTRESS historical controls (9%). The remaining participants had no recorded readmission or death within the 365-day follow-up period.

Table 6
Readmission and death before first recorded readmission within 365 days of index admission in FORTRESS Plus and FORTRESS historical controls: n (%)

| Outcome status at 365 days | FORTRESS Plus (n = 118), *n* (%) | FORTRESS (n = 110), *n* (%) |
|---|---|---|
| Censored, no readmission or death within 365 days | 48 (41%) | 44 (40%) |
| Death recorded before any readmission | 4 (3%) | 10 (9%) |
| Readmission within 365 days | 66 (56%) | 56 (51%) |

# Time to readmission and risk of any readmission

Time-to-event analyses did not identify a statistically significant difference between FORTRESS Plus and FORTRESS historical controls. The adjusted hazard ratio for the composite outcome of readmission or death was 1.15 (95% CI 0.80 to 1.65). For readmission with death treated as a competing event, the adjusted subdistribution hazard ratio was 1.28 (95% CI 0.88 to 1.86), and the adjusted cause-specific hazard ratio was 1.26 (95% CI 0.86 to 1.82).

There were no significant differences in the risk of any readmission within 365 days of index admission. Modified Poisson regression estimated an adjusted relative risk of 1.02 (95% CI 0.82 to 1.27) for the

binary outcome of any readmission or death and 1.12 (95% CI 0.87 to 1.45) for any readmission.

Table 7
Time-to-event for readmission and relative risk of any readmission within 365 days of index admission in FORTRESS Plus versus FORTRESS historical controls

| Event or outcome | Statistical method | Adjusted estimate (95% CI) |
|---|---|---|
| Time to event | | Hazard ratio in FORTRESS Plus vs FORTRESS |
| Readmission or death | Cox proportional hazards model | 1.15 (0.80 to 1.65) |
| Readmission with death as a competing event | Competing risk model: sub distribution hazard | 1.28 (0.88 to 1.86) |
| Readmission with death as a competing event | Competing risk model: cause-specific hazard | 1.26 (0.86 to 1.82) |
| Any readmission | | Relative risk in FORTRESS PLUS vs FORTRESS |
| Readmission | Modified Poisson regression | 1.12 (0.87 to 1.45) |
| Readmission or death | Modified Poisson regression | 1.02 (0.82 to 1.27) |

*Adjusted analyses included age, sex, hospitalisation during the preceding 12 months, baseline FRAIL score, and baseline MMSE score. Follow-up began at the index admission and was censored at 365 days. HR, hazard ratio; RR, relative risk; CI, confidence interval.*

# Number of readmissions and hospital nights

The number of readmissions and total hospital nights after readmission did not differ significantly between FORTRESS Plus and FORTRESS historical controls.

Table 8
Number of hospital readmissions and hospital nights within 365 days in FORTRESS Plus and FORTRESS historical controls

| Measure | FORTRESS Plus, *n* = 118 | FORTRESS historical controls, *n* = 110 | Kruskal-Wallis *p* |
|---|---|---|---|
| Number of readmissions | Mean 0.90 (95% CI 0.71 to 1.10); median 1 (IQR 0 to 1); range 0 to 5 | Mean 0.90 (95% CI 0.68 to 1.12); median 1 (IQR 0 to 1); range 0 to 5 | 0.80 |
| Hospital nights after readmission | Mean 7.9 (95% CI 4.7 to 11.0); median 1.0 (IQR 0 to 7); range 0 to 99 | Mean 10.0 (95% CI 6.1 to 13.8); median 1.5 (IQR 0 to 10); range 0 to 107 | 0.70 |

# Analyses within FORTRESS Plus intervention participants only (n = 141)

# Health-related quality of life

Within all FORTRESS Plus participants, adjusted mean EQ-5D-5L index scores increased from 0.48 at baseline to 0.70 at 4 months and 0.75 at 12 months. The adjusted mean change from baseline was 0.22 at 4 months and 0.27 at 12 months, with both changes statistically significant. The additional change between 4 and 12 months was not statistically significant.

EQ-5D VAS scores also increased within FORTRESS Plus. Adjusted mean scores increased by 8.5 points (95% CI 3.9 to 13.1) at 4 months and 12.6 points (95% CI 7.5 to 17.6) at 12 months, each compared with baseline. The additional change between 4 and 12 months was not statistically significant (4.1, 95% CI − 1.4 to 9.6).

Table 9
Adjusted means and change over time in health-related quality of life within FORTRESS Plus

| Outcome and cohort | Baseline, adjusted mean (95% CI) | 4-month follow-up, adjusted mean (95% CI); change from baseline (95% CI), *p* | 12-month follow-up, adjusted mean (95% CI); change from baseline (95% CI), *p* | Change from 4 to 12 months (95% CI), *p* |
|---|---|---|---|---|
| EQ-5D-5L index, full cohort, n = 141 | 0.48 (0.44 to 0.53) | 0.70 (0.64 to 0.75); 0.22 (0.15 to 0.28), $p < 0.0001$ | 0.75 (0.69 to 0.81); 0.27 (0.20 to 0.34), $p < 0.0001$ | 0.05 (− 0.02 to 0.13), $p = 0.15$ |
| EQ-5D VAS, full cohort, n = 141 | 58.5 (55.6 to 61.4) | 67.0 (63.2 to 70.8); 8.5 (3.9 to 13.1), $p = 0.0003$ | 71.1 (66.7 to 75.5); 12.6 (7.5 to 17.6), $p < 0.0001$ | 4.1 (− 1.4 to 9.6), $p = 0.14$ |

*Longitudinal mixed models were adjusted for ward, age, sex, baseline FRAIL score, baseline MMSE score, and hospitalisation during the preceding 12 months*

# Physical Function

SPPB scores improved progressively over time within FORTRESS Plus. The adjusted mean score increased from 5.6 at baseline to 7.3 at 4 months, representing a mean increase of 1.71 points, 95% CI 1.18 to 2.25, $p < 0.0001$. Scores increased further to 8.1 at 12 months, corresponding to a baseline-to-12-month increase of 2.47 points, 95% CI 1.88 to 3.06, $p < 0.0001$. The additional increase between 4 and 12 months was 0.76 points, 95% CI 0.17 to 1.35, p = .01.

Baseline SPPB data were missing for 59 participants because the assessment was conducted from the first home visit onward rather than during the acute hospital admission. No comparison with FORTRESS historical controls were available for SPPB.

# Mood

GDS-15 scores decreased progressively over time within FORTRESS Plus. The adjusted mean score decreased from 4.75 at the first home visit to 3.66 at 4 months and 2.88 at 12 months. The adjusted

mean change from baseline was − 1.10 points at 4 months (95% CI − 1.73 to − 0.46; $p = 0.0008$) and − 1.87 points at 12 months (95% CI − 2.56 to − 1.18; $p < 0.0001$). The additional reduction between 4 and 12 months was − 0.77 points (95% CI − 1.46 to − 0.09; $p = 0.03$).

Baseline GDS-15 data were also collected at the first home visit and were missing for 59 participants who did not complete the first home visit. No comparison with FORTRESS historical controls was available for GDS-15.

## Social support

Social support data were available for 75 of 141 FORTRESS Plus participants (53%). Among participants with available data, 57 (76%) reported at least some support, while 18 (24%) reported having no significant other. Responses were bimodal, with participants typically reporting either very supportive circumstances or no significant other. The mean support level was 2.7 (95% CI 2.2 to 3.1), between somewhat supportive and quite supportive, and the median was 3.7 (IQR 0.5 to 4.0), between quite supportive and very supportive.

## Medication burden

DBI was assessed at baseline and 12 months and was not collected at the 4-month assessment. Within FORTRESS Plus, the adjusted mean DBI score decreased from 0.50 at baseline (95% CI 0.39 to 0.62) to 0.43 at 12 months (95% CI 0.30 to 0.55). The adjusted mean change was − 0.08 (95% CI − 0.14 to − 0.01; $p = 0.01$). This was a within-cohort change and cannot be attributed solely to pharmacist review or deprescribing recommendations. No comparative data for FORTRESS historical controls were available for DBI scores.

# DISCUSSION

The more intensive multicomponent intervention delivered in FORTRESS Plus was associated with improved health-related quality of life compared to the less intensive intervention delivered in the FORTRESS study. Longitudinal modelling and causal inference approaches using inverse probability weighting (IPW) both supported this finding. Health-related quality of life improved among FORTRESS Plus participants over follow-up, whereas it remained stable in FORTRESS historical controls. Physical function and depressive symptoms also improved within FORTRESS Plus, but these outcomes were not available for comparison in FORTRESS. In contrast, the FORTRESS Plus intervention was not associated with lower hospital readmission risk or a lower risk of readmission or death when compared with the FORTRESS intervention. This is not necessarily inconsistent with the improvement in health-related quality of life: EQ-5D-5L captures perceived health and functioning, whereas readmission is influenced by acute exacerbations, multimorbidity, mortality, discharge pathways, access to community care and thresholds for hospital use.

The observed difference between cohorts is consistent with evidence that the dose and intensity of community-based exercise influences outcomes in frail older adults. In randomised dose comparisons, frail participants reported improved health-related quality of life only at higher exercise doses [19], and meta-regression of trials in frail and pre-frail adults indicates that at least two supervised sessions per week are required to improve physical performance, with further gains at three [20]. Higher-intensity progressive resistance training produces larger strength and functional gains than low-moderate intensity programmes in frail older adults [21, 22]. This contrasts with the low intensity of usual care observed in the audit underpinning this study, in which progressive resistance training was delivered in only 23% of admissions [4], providing important context for interpreting the additional evidence from FORTRESS Plus.

Minimally clinically important differences (MCID) for EQ-5D index scores vary substantially across studies, estimation methods, and populations, and no MCID has been established for the Australian EQ-5D-5L value set in this population. In the falls population studied by Jehu et al., estimates ranged from 0.028 to 0.090 depending on the anchor the estimation method used and were derived for the three-level rather than five-level index [23]. Against this variable background, the adjusted between-cohort differences of 0.17 to 0.24 observed here exceed the upper end of those estimates and the mean estimates reported in the systematic review of EQ-5D MCIDs [24] and are therefore very likely to represent clinically meaningful improvement.

These findings should also be considered alongside the broader transitional care literature. A systematic review of 25 randomised trials of hospital-to-home transitional care interventions in older adults found that multicomponent interventions were frequently associated with improvements in functional status and mood and with modest short-term reductions in readmissions, but sustained effects were uncommon and few trials assessed outcomes beyond six months [25]. Against this background, the improvement of approximately 0.17 to 0.24 points in EQ-5D-5L index score in FORTRESS Plus, sustained to 12 months, compares favourably with the short-lived and predominantly functional and mood-related effects reported in randomised transitional care trials, although the non-randomised design of FORTRESS Plus means that unmeasured residual confounding cannot be completely excluded. The absence of a reduction in readmissions is consistent with the variable effects of transitional care interventions on hospital use reported in that review [25], although a recent meta-analysis of comprehensive geriatric assessment trials found reduced readmission rates at six months [26]; differences in intervention intensity, populations, and follow-up duration may partly explain this discrepancy.

The pattern for self-rated health was weaker than for the EQ-5D-5L index. EQ-5D VAS scores were higher in FORTRESS Plus than in FORTRESS historical controls at both 4 and 12 months, and the overall time-by-study interaction was statistically significant ($p = 0.049$). However, this difference did not progressively widen: the adjusted between-group difference was 13.4 points at 4 months and 12.7 points at 12 months, and the baseline-to-12-month interaction was not statistically significant ($p = 0.061$). The

results are therefore consistent with a difference that emerged by 4 months and was maintained to 12 months.

SPPB and GDS-15 scores also improved within FORTRESS Plus. SPPB scores increased and GDS-15 scores decreased over follow-up. There was no historical comparison for either measure, and baseline assessments were missing for 59 participants. These findings should therefore be interpreted as within-cohort changes only. They may reflect the intervention, recovery from acute illness, selective participation in home visits, or other changes over follow-up, and do not establish the presence of a causal effect.

The FRAIL scale was used for eligibility screening and baseline adjustment rather than as a repeated outcome. Changes in frailty status across follow-up were therefore not assessed, and no conclusions are drawn about whether FORTRESS Plus changed frailty. DBI scores decreased between baseline and 12 months within the FORTRESS Plus cohort, and there was no historical comparison. This finding is therefore descriptive and cannot be attributed solely to pharmacist review or deprescribing.

Exposure to the inpatient components of the intervention was high, with pharmacy review received by 140 of 141 participants and comprehensive geriatric assessment completed by 127 (90.1%). The post-discharge exercise programme was received by 84 of 141 participants (59.6%). Among those who received it, adherence was high, with a median of seven supervised home visits attended and 62 of 84 (73.8%) rated very or quite adherent by the treating Exercise Physiologist. High adherence among participants who received the programme supports the interpretation of the health-related quality-of-life findings, but incomplete uptake means the intervention effect applies to those who participated in the post-discharge component. Selective uptake may also limit interpretation of the within-cohort changes in physical function and mood, and the outcome assessor was not blinded to intervention exposure. Twenty participants died during the study period, none judged related to the intervention.

# Strengths and limitations

Intervention exposure, adherence, and adverse events were systematically recorded. The primary outcome finding was supported by complementary secondary and sensitivity analyses, including longitudinal modelling and causal inference methodology for non-randomised data, and statistical approaches were used that accounted for missingness in follow-up data, death after baseline, and baseline imbalance in measured confounders.

The main limitation in the comparative analyses was that randomisation was not possible in the context of a historical control group. The FORTRESS Plus and FORTRESS studies recruited during different calendar periods and may have differed in usual care, staffing, discharge pathways, and other factors that were not measured. In the absence of randomised treatment assignment, unmeasured residual confounding in the comparison between FORTRESS Plus intervention participants and FORTRESS historical controls cannot be completely excluded.

Attrition was substantial, with follow-up data available for only 48 FORTRESS Plus participants involved in the comparative study at 12 months. Missing follow-up may have been related to functional decline, hospitalisation, or mortality. Consequently, survivor-only and complete-case analyses may not represent outcomes in the full recruited population, thus statistical approaches were used to account for missing follow-up in longitudinal modelling, and data imputation was undertaken before applying causal inference analyses for non-randomised data, including sensitivity analyses of alternative methods for handling death as an outcome.

Other limitations include the lack of historical comparator data for SPPB, GDS-15 and DBI outcomes, and substantial missing data at baseline from the home-visit assessments for SPPB and GDS-15. Within-study changes in SPPB and GDS-15 scores in FORTRESS Plus are not sufficient to establish the presence of a causal effect of the intervention, in the absence of a concurrent control group, and the missing data on SPPB and GDS-15 at baseline increase risks of bias in the analyses of those outcomes. The Exercise Physiologist delivered the intervention and conducted follow-up assessments and was therefore not blinded to intervention exposure, which may have introduced ascertainment bias in participant-reported outcomes. Finally, the study was conducted at a single hospital with an opt-out consent process and required sufficient English to participate, which may limit generalisability to other settings.

# Implications

These findings support further evaluation of FORTRESS Plus. In this non-randomised study, the intervention was associated with greater improvement in health-related quality of life than the less intensive historical intervention. Improvements in physical function and mood were observed within the FORTRESS Plus cohort, but these findings cannot yet be attributed to the intervention itself because these outcomes were not compared with historical controls. The study did not demonstrate a reduction in hospital readmissions.

The historical-control design limits causal interpretation because differences between cohorts, including unmeasured factors, may have influenced the results. A future randomised study with a concurrent comparator would better distinguish intervention effects from recovery after acute illness and changes in care over time. Future evaluations should also use blinded outcome assessment where feasible, collect baseline physical-function and mood measures, and improve follow-up completeness.

The intervention delivered in FORTRESS Plus requires staff time for up to seven weekly, supervised home exercise visits by an Exercise Physiologist, in addition to inpatient multidisciplinary care. A prospective economic evaluation of intervention costs, healthcare utilisation, and quality-adjusted life-years is needed to assess whether this delivery model is cost-effective.

## CONCLUSION

The multicomponent frailty intervention delivered in FORTRESS Plus was associated with improvements in health-related quality of life based on EQ-5D-5L index scores which were not found for the less

intensive community-based FORTRESS study intervention. Physical function and depressive symptoms improved within the FORTRESS Plus cohort, although these outcomes were not compared with historical controls. There was no evidence that the FORTRESS Plus intervention reduced hospital readmissions. These findings support evaluation in a randomised trial of FORTRESS Plus versus current usual post-discharge care.

# Abbreviations

ATE: average treatment effect
CI: confidence interval
DBI: Drug Burden Index
EMR: electronic medical record
EQ-5D-5L: EuroQol 5-dimension, 5-level questionnaire
FMP: Frailty Management Plan
FORTRESS: Frailty in older people: Rehabilitation Treatment Research Examining Separate Settings
FORTRESS Plus: Frailty in older people: Rehabilitation Treatment Research Examining Separate Settings Plus
G-MEDSS: Goal-directed Medication review Electronic Decision Support System
GDS-15: 15-item Geriatric Depression Scale
IQR: interquartile range
MCID: Minimally clinically important difference
MMSE: Mini-Mental State Examination
SD: standard deviation
SMMSE: Standardised Mini-Mental State Examination
SPPB: Short Physical Performance Battery
VAS: visual analogue scale

# Declarations

### Ethics approval and trial registration

Informed consent was not obtained from individual participants: the requirement for individual written informed consent was waived by the Northern Sydney Local Health District Human Research Ethics Committee, which approved an opt-out recruitment process. This study was approved by the Northern Sydney Local Health District Human Research Ethics Committee (2023/ETH00649) and received site-specific governance approval (2023/STE01740). FORTRESS Plus was registered with the Australian New Zealand Clinical Trials Registry, ACTRN12623001103651, on 20 October 2023. All procedures were performed in accordance with the relevant institutional and national guidelines and regulations, and in accordance with the Declaration of Helsinki.

### Consent for publication

Not applicable. This manuscript does not contain individual-level identifying data, images or videos.

**Availability of data and materials**

The datasets generated and/or analysed during the current study are not publicly available because they contain participant health information and are subject to ethics and governance restrictions. De-identified data may be available from the corresponding author on reasonable request, subject to approval from the relevant ethics committee and data custodians.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

AK conducted the statistical analysis and interpreted the findings. RT interpreted findings and drafted the manuscript. All authors (RT, AK, CP, JM, IC and SK) contributed to interpretation of findings and critical revision of the manuscript and read and approved the final version.

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# Figures

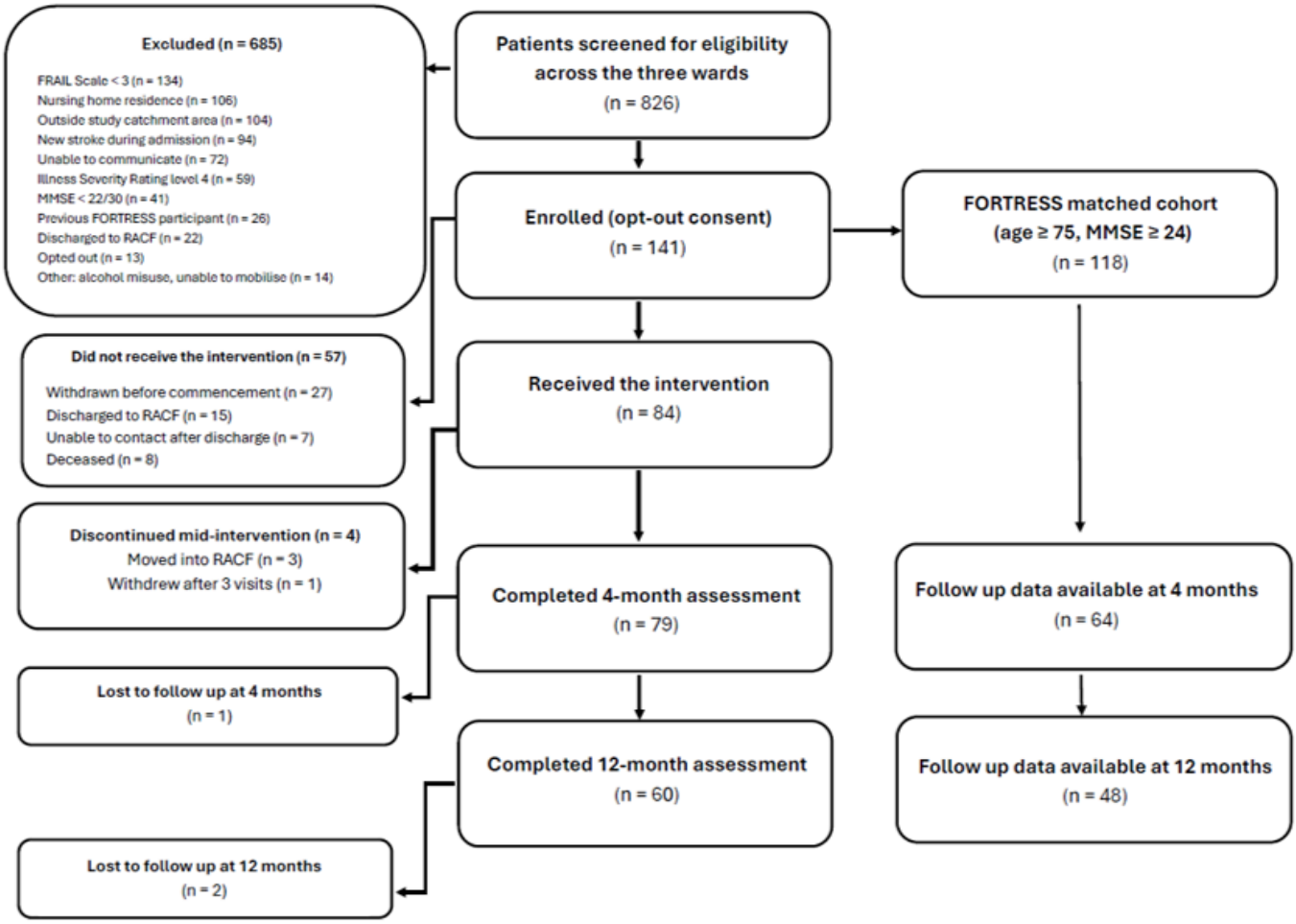



**Figure 1**

**Participant flow through the FORTRESS Plus study**

*MMSE, Mini-Mental State Examination; RACF, residential aged care facility. The comparative study cohort comprises FORTRESS Plus participants who met the original FORTRESS eligibility criteria (age ≥ 75 years, MMSE ≥ 24), analysed against 110 historical controls from the FORTRESS intervention arm*

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TRENDchecklistFORTRESSPlus.docx
- smmseguidelinesihacpa.pdf