# Integrated Geriatric Assessment and Treatment Effectiveness (INTEGERATE) in older people with cancer starting systemic anticancer treatment in Australia: a multicentre, open-label, randomised controlled trial

# Protocol and Statistical Analysis Plan

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# INTEGERATE
# Is INTEgrated GERiatric Assessment and Treatment Effective in older adults with cancer receiving chemotherapy?
# A Randomised Controlled Study

# Protocol

**Version: 2.0**

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**INTEGERATE: Is INTEgrated GERiatric Assessment and Treatment Effective in older adults with receiving chemotherapy? A randomised controlled study**


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# Statement of Compliance

This study will be conducted in accordance with the design and specific provisions of this Independent Ethics Committee (IEC) approved protocol, in accordance with the ethical principles of the National Statement on Ethical Conduct in Human Research, 2007 published by the National Health & Medical Research Council (NHMRC) and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirement(s). The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the IEC, except where necessary to eliminate an immediate hazard(s) to the study participants. The Principal Investigator will promptly report to the IEC any changes in research activity and all unanticipated problems involving risk to human subjects, or others.

# Contents

# INTEGERATE Synopsis

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| **TITLE** | INTEGERATE – Is INTEgrated GERiatric Assessment and Treatment Effective in older adults receiving chemotherapy? A randomised controlled study. |
| **SPONSOR** | Eastern Health (Investigator initiated) |
| **INDICATION** | Older adults with solid organ cancer or diffuse large B-cell lymphoma |
| **RATIONALE** | Older adults with cancer receiving chemotherapy are particularly vulnerable to adverse effects of cancer and cancer therapy due to the presence of underlying co-morbidities, functional and psychosocial issues. Integrated geriatric care offers a comprehensive, coordinated team approach to care. This may lead to improved quality of life and other key clinical outcomes in older adults with cancer. |
| **AIM** | The aim of this prospective, randomised controlled study is to evaluate the effects of integrated geriatric care on quality of life and other key clinical outcomes in in older adults with cancer receiving chemotherapy. |
| **OBJECTIVES** | Primary Objectives<br>• Assess the effects of integrated geriatric care on health-related quality of life (HRQoL) in older adults with cancer receiving chemotherapy<br><br>Secondary Objectives<br>• Assess the effects of integrated geriatric care on survival, function, mood, nutrition, health utilities, chemotherapy delivery, healthcare utilisation and institutionalisation<br><br>Exploratory Objectives<br>• Perform a comparative economic evaluation of integrated geriatric care compared to standard oncology care<br>• Evaluate the interventions that result from integrated geriatric care<br>• Evaluate the relationship between components of HRQoL and comprehensive geriatric assessment (CGA) with clinical outcomes<br>• Develop a brief geriatric assessment screening tool and predictive model for older adults with cancer<br>• Compare the EORTC QLQ-C30 and QLQ-ELD14 with the EQ-5D-5L<br><br>**Psychometric Evaluation Sub-Study**<br>• Evaluate the relative statistical efficiency of the Trial Outcome Index (TOI) against its component scales<br>• Confirm the reliability and validity of the TOI in the study population<br>• Estimate the Minimal Important Difference (MID) for clinical significance of the TOI |
| **STUDY DESIGN** | Prospective, randomised, two-arm, open-label, controlled, parallel group, superiority study |
| **NUMBER OF PATIENTS** | A planned total of approximately 128 evaluable patients will be enrolled into the study |
| **TARGET POPULATION** | Patients aged ≥70 years with cancer receiving chemotherapy |
| **INCLUSION CRITERIA** | Patients must meet ALL of the following criteria in order to be eligible for this study:<br>1. Aged ≥70 years<br>2. Pathologically confirmed solid organ cancer or diffuse large B-cell lymphoma<br>3. Planned for cytotoxic chemotherapy, targeted therapy or immunotherapy<br>4. Able to effectively understand the language of the HRQoL questionnaires in one of the validated languages for the questionnaires<br>5. Able to give written informed consent before randomisation according to local, national and international regulations |
| **EXCLUSION CRITERIA** | Patients who meet any ONE of the following criteria are not eligible for this study:<br>1. Have received cytotoxic chemotherapy, targeted therapy or immunotherapy within 3 months prior to enrolment<br>2. Unable to self-complete the HRQoL questionnaires<br>3. Any condition (e.g. psychological, geographical, etc.) that does not permit compliance with the protocol<br>4. Prior enrolment in this study |
| **LENGTH OF STUDY** | The total study duration, from the first patient recruited to the time of the primary analysis, is approximately 36 months: approximately 30 months of recruitment and |

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| | approximately 6 months of follow-up for the last patient recruited. |
| **INTERVENTION** | Integrated geriatric care |
| **CONTROL** | Standard oncology care |
| **ALLOCATION** | By the method of minimisation, stratified according to the following characteristics:<br>• treatment intent<br>• tumour type<br>• age<br>• gender<br>• ECOG performance status (physician-rated) |
| **ASSESSMENTS** | Primary endpoint:<br>• Trial Outcome Index (TOI), which consists of the linear transformation from 0 to 100 of the unweighted summated scores of the physical functioning (PF2), role functioning (RF2) and social functioning (SF) scales of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, and the mobility (MO) scale of the EORTC QLQ-ELD14 questionnaire. This represents the physical and functional aspects of quality of life, which are fundamental indicators of the overall impact of illness and treatment on an elderly person's quality of life.<br><br>Secondary endpoints:<br>• Function, as assessed by self-rated performance status (ECOG, Karnofsky), Katz Activities of Daily Living (ADL) and Older American Resources and Services (OARS) Independent Activities of Daily Living (IADL)<br>• Overall survival, defined as time from randomisation to death from any cause<br>• Mood, as assessed by the Patient Health Questionnaire 9-item (PHQ-9) and Generalized Anxiety Disorder 7-item (GAD-7)<br>• Nutrition, as assessed by the self-Mini Nutritional Assessment (self-MNA)<br>• Chemotherapy delivery, as assessed by chemotherapy dose, dose adjustments, delays or discontinuation<br>• Healthcare utilisation, as assessed by emergency department visits, hospital admissions, medical consultations and type of PBS-listed medications.<br>• Institutionalisation, as assessed by place of residence and level of care<br>• Health utilities, as assessed by the EQ-5D-5L |
| **PROCEDURES (Summary)** | Eligible and consenting patients will complete patient-reported outcome (PRO) measures of HRQoL, function, mood, nutrition and social situation; and timed-up-and-go test (TUG) at enrolment (prior to randomisation). All participants will receive brief generic advice about nutrition and activity and will be given the Cancer Council of Victoria's booklet on "Understanding Chemotherapy: a guide for people with cancer, their families and friends".<br><br>Following completion of baseline assessment, participants will be randomised to either intervention or control arm:<br>• Intervention arm: Participants receive integrated geriatric care, which involves comprehensive geriatric assessment and management. In addition, participants continue to see their oncologist. The treating clinicians are able to review results from the assessments, except for the HRQoL questionnaires (because it will be used to calculate the primary outcome measure). Participants complete the test-retest assessment at day 7 (if not yet commenced chemotherapy). Assessment of outcome measures occurs at 12 weeks, 18 weeks and 24 weeks following randomisation. After 24 weeks, participants may continue to receive integrated geriatric care but will not be required to complete further study assessments.<br>• Control arm: Participants receive standard oncology care provided by their oncologist. The treating clinicians are blinded to the results of the assessments. Participants complete test-retest form at day 7 (if not yet commenced chemotherapy). Assessment of outcome measures occurs at 12 weeks, 18 weeks and 24 weeks following randomisation. After 24 weeks, |

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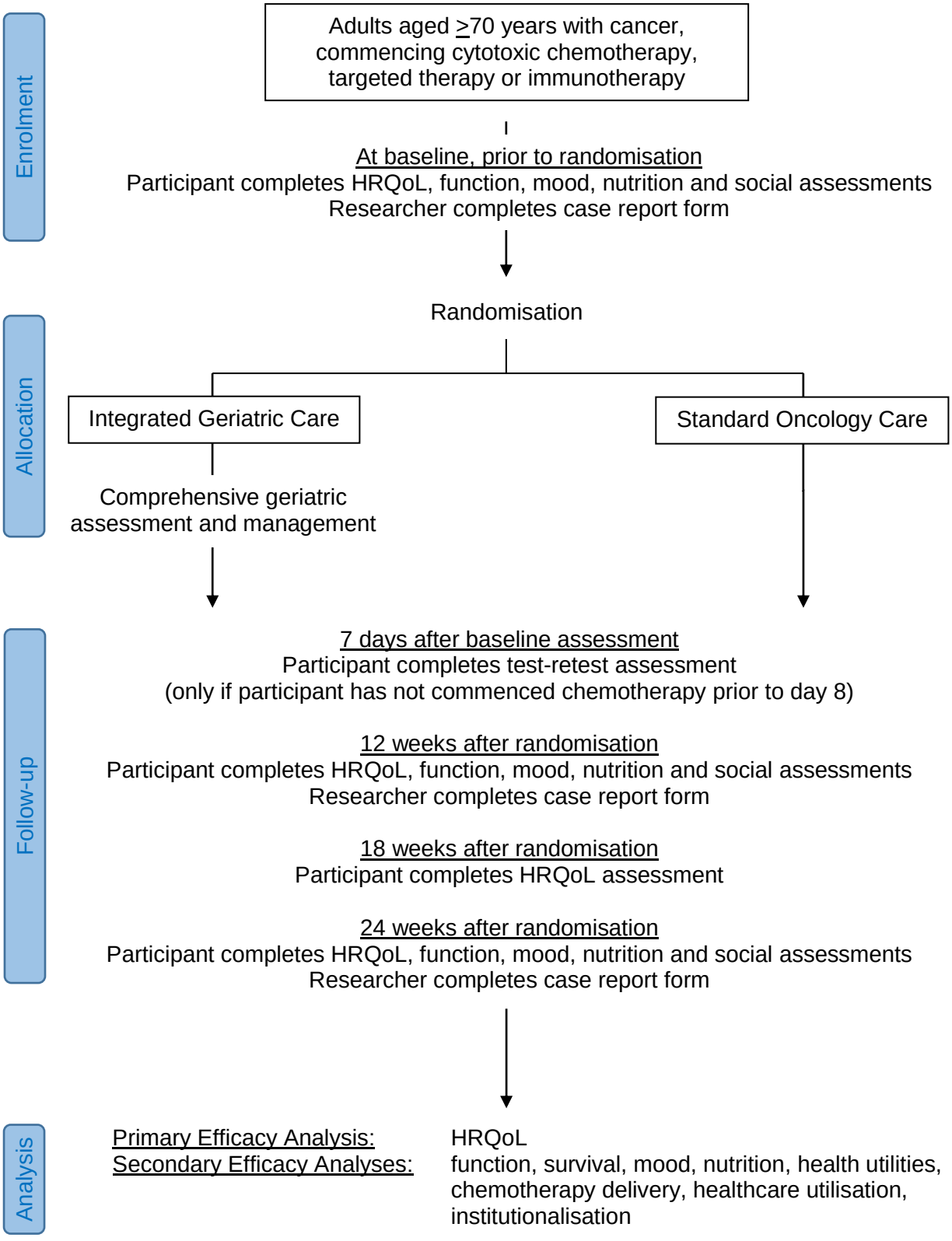
| | participants will no longer be required to complete further study assessments. Although participants in the control arm may be referred to a geriatrician at any time, they will not be permitted to cross-over to receive the study-specific comprehensive geriatric assessment and management. |
| **STATISTICAL ANALYSES** | **PRIMARY EFFICACY ANALYSIS**<br>The primary efficacy analysis will address the primary objective of the study which is to assess the effects of integrated geriatric care on HRQoL in older adults with cancer receiving chemotherapy. This will involve a hierarchical set of HRQoL analyses.<br><br>The primary HRQoL analysis will to compare the longitudinal change in TOI score for significant between-group difference using linear mixed models. Sensitivity analyses will be performed using pattern-mixture models and/or joint model of longitudinal and survival data if greater than 20% of TOI data are missing and if the reasons for missing data and patterns of missing data are not missing at random.<br><br>The secondary HRQoL analyses will compare: i) the proportion of participants who experience change in TOI by at least the clinically important threshold, using Fisher's test; and ii) time to change in TOI by at least the clinically important threshold using log-rank test.<br><br>The tertiary HRQoL analyses involve analyses using t-test or Wilcoxon test (according to normality of distribution) of all the scales of the EORTC QLQ-C30, QLQ-ELD14 and EQ-5D-5L, to complement the primary and secondary HRQoL analyses, to make full use of all HRQoL data collected and to assist in interpretation of the of the primary endpoint.<br><br>**Sample Size Calculation**<br>The target sample for this study is based on an independent t-test at a 2-sided significance level of 0.05 to have an 80% power to detect a significant between-group difference in TOI from baseline to 12 weeks with an effect size of 0.5. Under these assumptions, a minimum sample size of 64 evaluable participants in each group (or a total of approximately 128 evaluable participants) who have completed the HRQoL questionnaires at baseline and 12 weeks is required. |

# Schematics of Study Design



# Abbreviations

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| ACAS | Aged Care Assessment Service |
| ADL | Activities of Daily Living |
| CES-D | Center for Epidemiologic Studies Depression scale |
| CGA | comprehensive geriatric assessment |
| CRASH | Chemotherapy Risk Assessment Scale for High-Age Patients |
| CRF | case report forms |
| DSM-IV-TR | Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision |
| ECOG | Eastern Cooperative Oncology Group |
| EORTC | European Organisation for Research and Treatment of Cancer |
| FACT | Functional Assessment of Cancer Therapy |
| fTRST | Flemish version of Triage Risk Screening Tool |
| GAD-7 | Generalized Anxiety Disorder 7-item |
| GCP | Good Clinical Practice |
| HR | hazard ratio |
| HRQoL | health-related quality of life |
| IADL | Instrumental Activities of Daily Living |
| ICER | Incremental Cost-Effectiveness Ratio |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| KPS | Karnofsky Performance Status |
| MAUI | Multi-attribute utility instruments |
| MID | Minimal Important Difference |
| MMSE | mini-mental status examination |
| MNA | mini-nutritional assessment |
| MOS | Medical Outcome Survey |
| MoCA | Montreal Cognitive Assessment Test |
| NCIC CTG | NCIC Clinical Trials Group |
| NHMRC | National Health & Medical Research Council |
| OARS | Older American Resources and Services |
| PBAC | Pharmaceutical Benefits and Advisory Committee |
| PBS | Pharmaceutical Benefits Scheme |
| PHQ-9 | Patient Health Questionnaire 9-item |
| PICF | Participant Information and Consent Form |
| PoCoG | Psycho-oncology Co-operative Research Group |
| PRO | patient-reported outcome |
| QALY | quality-adjusted life years |
| QLQ | Quality of Life Questionnaire |
| QoL | quality of life |
| SAP | Statistical Analysis Plan |
| SPIRIT | Standard Protocol Items: Recommendations for Interventional Trials |
| TOI | Trial Outcome Index |
| TUG | Timed-Up-and-Go test |

# 1. Background & Rationale

## 1.1. Background Information

### 1.1.1. Cancer in older adults

Cancer occurs primarily in older individuals.(1) In Australia, the majority of cancer already occurs in those aged 65 years and older and is often diagnosed in advanced stages.(2) The proportion of the population aged 65 years and older is projected to rise from 13.6% in 2010 to around 23% by 2050.(3, 4) The ageing population is expected to contribute to a projected 56% increase in Australian annual cancer incidence from 108,836 in 2007 to 170,000 by 2025, with adults 65 years and older accounting for over 80% of the increase.(5) The outer eastern area of Melbourne, in particular, is expected to experience a higher growth of older persons than metropolitan Melbourne and Victoria; which in turn suggests a greater burden of age-related diseases such as cancer.(6) In addition, although overall mortality risk from cancer is decreasing, these trends are not as evident for older patients.(7)

Older adults with cancer are particularly vulnerable to adverse effects of cancer or cancer therapy. The ageing process itself is associated with physiological changes that reduce functional reserves. In addition, older adults are more likely to experience issues related to comorbidities, polypharmacy, functional dependence, socioeconomic status, nutrition, mood and cognitive disorders. These vulnerabilities are particularly enhanced by chemotherapy and in turn increases the risk of chemotherapy toxicity. Improved identification of underlying issues and implementation of coordinated interventions to optimise the support and health of this group of at-risk patients may lead to improved outcomes.

### 1.1.2. Comprehensive geriatric assessment

Within the international geriatric oncology community, the development of healthcare delivery based on an integrated oncogeriatric approach has emerged as a top priority.(8) Three core aspects of the integrated oncogeriatric approach are: geriatric assessment, comorbidity burden and treatment outcomes.(8) For its successful implementation, the two broad pre-conditions are: coordinated healthcare delivery and primary supportive care services.(8)

Geriatric assessment can take many different forms, with comprehensive geriatric assessment (CGA) representing the most extensive form of geriatric assessment. CGA is a multidimensional, usually interdisciplinary, diagnostic process to quantify an elderly individual's medical, psychological, and functional capabilities in order to develop a coordinated and integrated plan for treatment and long-term follow-up.(9, 10) It has two essential components: the process of evaluation coupled to an appropriate management plan.(10) It differs from a standard medical evaluation in that CGA provides a more detailed evaluation of elderly individuals with complex problems by utilising an interdisciplinary team approach and emphasising function and quality of life. CGA should include an evaluation of comorbidities, socioeconomic issues, nutritional status, polypharmacy, functional dependence, emotional and cognitive conditions, an estimate of life expectancy, and recognition of frailty.(11) In many settings, the CGA process relies on a core team consisting of a physician, nurse, and social worker and, when appropriate, draws upon an extended team of physical and occupational therapists, nutritionists, pharmacists, psychiatrists, and psychologists. Increasingly, CGA programs are moving towards a "virtual team" concept in which members are included as needed, assessments are conducted at different locations on different days, and team communication is completed via telephone or electronically.(12) There is also increasing use of validated self-reported assessment instruments to reduce time and resource burden on clinicians and help target the evaluation to specific areas of concern.

## 1.1.3. Evidence for comprehensive geriatric assessment in oncology

Since the emergence of the concept of geriatric oncology in the 1980s, numerous clinical trials around the world have examined the role of geriatric assessment in older cancer patients in four different aspects: detection of geriatric problems; the prognostic and predictive value of the geriatric variables; its influence on treatment decisions; and the therapeutic impact of geriatric assessment on clinical outcomes.

There is strong evidence that CGA is feasible and detects many problems that are frequently unrecognised or inadequately addressed in general geriatric and cancer patients.(13) From the Australian perspective, in the first 200 patients seen in the geriatric oncology program of the Royal Adelaide Hospital, 40% had significant functional impairment, 26% had greater than three comorbidities and 38% had $\geq$5 medications (polypharmacy), 34% had significant weight loss and 20% reported falls and memory concerns.(14) In another study from a regional Australian centre reported as an abstract at the 12$^{th}$ International Society of Geriatric Oncology Meeting, implementation of a screening geriatric oncology assessment tool in newly diagnosed cancer patients aged over 70 years was found to be feasible, took about 20 minutes and cost about AUD$42 per patient.(15) The screening program resulted in the referral of 57% of patients to supportive care services, including cancer care coordination (23%), carer support organisation (11%), palliative care (12%), home and community care (10%) community allied (4%) and district nurse (2%).

Components of the CGA (e.g. comorbidity, functional status, geriatric syndrome, nutritional status) have high prognostic value for predicting morbidity and mortality in older adults.(16-20) In addition, two recent large studies developed models for predicting chemotherapy toxicity in older adults with cancer which includes geriatric variables. In the model developed by the Cancer and Aging Research Group, the geriatric variables that predicted chemotherapy toxicity included: age $\geq$72 years, hearing impairment, history of falls, dependence on medication administration, limitation in mobility and decreased social activity.(21) In another model known as the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score, the geriatric variables that predicted chemotherapy toxicity in patients aged $\geq$70 years included: dependence in instrumental activities of daily living (IADL), impaired mini-mental status examination (MMSE) score and impaired mini-nutritional assessment score (MNA).(22) Both chemotherapy toxicity prediction models are currently undergoing external validation.

Geriatric assessment can also influence treatment decisions with two published studies demonstrating that geriatric assessment prior to chemotherapy led to modification in chemotherapy regimen in 39-50% of patients.(23, 24) In one study of 161 patients, pre-chemotherapy geriatric consultation resulted in 76% of patients undergoing some form of geriatric intervention and 49% of patients having modification of the initially proposed chemotherapy regimen – these modifications consisted of higher intensity therapy in 28%, lower intensity therapy in 18% and delayed therapy in 3%.(23)

In terms of the impact of geriatric assessment on outcomes in older adults with cancer, the evidence remains inconclusive due to a lack of randomised controlled trial data to date. One randomised trial addressed short-term nurse-delivered geriatric intervention in post-surgical cancer patients.(25) The 2-year survival for the advanced-stage disease group was 67% in the intervention group, compared with 40% in the control group (Hazard ratio (HR) for mortality 0.49, *P*=0.001). However, no difference was seen in the early-stage disease group. A recent non-randomised prospective cohort study of 135 older adults with cancer looked at the impact of geriatrician-delivered CGA on chemotherapy toxicity and tolerance.(26) Participants in the intervention cohort underwent risk-stratification using a patient-completed screening questionnaire and high-risk patients received a geriatrician-delivered CGA. Participants in the intervention group were more likely to complete treatment as planned (odds ratio (OR) 4.14 (95% CI: 1.50-11.42), *P*=0.006) and fewer required treatment modification (OR 0.34 (95% CI: 0.16-0.73), *P*=0.006).

Whilst there was a trend for fewer in the intervention group to develop grade 3+ toxicity, this did not reach statistical significance.

Whilst the above studies suggest a potential for CGA to improve outcomes in older adults with cancer, no randomised controlled trial testing the hypothesis that CGA can improve outcomes in the chemotherapy setting has yet been published. In particular, no randomised controlled study has examined the impact of CGA on quality of life, which is an important consideration for an older adult with cancer.(27) Randomised studies are therefore required to evaluate the benefits of geriatric assessment and intervention in terms of improving clinical outcomes for the effective translation of the integrated oncogeriatric approach into routine clinical practice.

# 1.2. Study Rationale

## 1.2.1. Rationale for incorporating comprehensive geriatric assessment in oncology

In oncology, treatment decisions and outcomes are influenced by patient characteristics, disease biology, treatment profile and patient preference for treatment. In older adults, patient characteristics become more important in treatment decisions due to decreased physiological reserves and increased likelihood of comorbidities, functional and psychosocial issues which impact on treatment delivery and tolerance. However, ageing is a highly individual process and older people – even at the same chronological age – have wide variability in their physical, mental and social health status. Therefore, integrating geriatric assessment into routine care of older adults with cancer can help tailor treatment plans to the individual and potentially lead to improved clinical outcomes in terms of quality of life (QoL) and even possibly patient survival.

The prevalence of age-related problems increases sharply after age 70 years, and therefore the International Geriatric Oncology Society has recommended that all cancer patients aged 70 years and older should receive some form of geriatric assessment.(13) The likelihood of age-related problems interacting with treatment is greater also for patients who are planned for treatment with high risk of adverse effects, such as chemotherapy, or for patients with advanced-stage cancer where progression of the cancer can unmask the underlying functional and psychosocial vulnerabilities of the patient.

At the minimum, performing a CGA would result in comprehensive documentation of the individual's physical, functional and psychosocial status at that point in time from which to inform clinical decision-making. A CGA might identify a group of patients who are "fit" who should receive full dose-treatment, a "vulnerable" group of patients who should be subject to some precautions (e.g. chemotherapy dose modification) and a group of patients who are too "frail" for treatment that aims to prolong life who should receive supportive care only.(28) For the vulnerable group of patients, interventions should be tailored to maximise the effective dose and minimise toxicity; this may include modification of treatment regimen and optimisation of their health status to improve chemotherapy tolerance.

The benefit of an integrated oncogeriatric approach is likely to lie beyond that of performing a CGA alone. Appropriate intervention should follow the assessment. Integrated geriatric care offers a comprehensive, coordinated team approach to care, with a different set of perspectives and interventions compared to standard oncology care. One of the primary foci in geriatric care is optimising function and QoL. It can also provide assistance to both patients and their families in dealing with physical, emotional and practical aspects of their treatment and disease. The benefits of geriatric care for cancer patients may occur as a direct effect of interventions (e.g. optimisation of functional abilities, better symptom control and better psychosocial support) or indirectly through its influence on cancer treatment decisions. Optimal management of co-morbid conditions could improve tolerance of cancer therapy and reduce non-cancer related mortality, particularly in the adjuvant treatment setting. In addition, effective coordination of the broad range of supportive care resources available through the hospital network (e.g. allied health services, rehabilitation programs) and community services (e.g. aged care services, palliative care) is likely to be an improvement on the current situation where their accessibility depends in part on the capacity of the patient to activate them.

In summary, older adults are particularly vulnerable to adverse effects of cancer and cancer therapy during cancer treatment due to the presence of underlying co-morbidities, and functional and psychosocial issues. An integrated oncogeriatric approach could potentially improve outcomes in this at-risk group. Randomised controlled trial data are currently lacking and are necessary for the translation of geriatric oncology concepts from the academic research setting into routine clinical practice. The present study seeks to address the current gap in knowledge by evaluating the effect of integrated geriatric care on key clinical outcomes in older adults with cancer receiving chemotherapy.

## 1.2.2. Rationale for health-related quality of life (HRQoL) assessment

Quality of life (QoL) is an important consideration for older adults with cancer. Older patients are less willing to compromise their QoL for the potential of increased survival and patients with incurable disease may prefer QoL above quantity of life, especially if treatment impacts on their functional capacity or cognition.(29) Almost three-quarters of older patients would rather die sooner than experience severe functional decline.(29) The aspects of QoL that are mentioned by patients aged 75 years and older to be important are: mobility (100%), personal care (65%), shopping (38%), household (35%), hobbies/pastime (32%), driving (26%), religion (16%), self-confidence (13%), family (6%), being free from pain (6%) and working (6%).(30)

The term health-related quality of life (HRQoL) is often used to restrict its context to the aspects of QoL related to health and healthcare.(31) HRQoL is a multidimensional concept that represents the patient's perception of the effect of illness and treatment on physical, psychological, and social aspects of life.(32) There are two basic types of HRQoL instruments: generic and disease-specific. Generic instruments focus on the main components that constitute HRQoL, and they are intended to be applied in a wide range of populations and health states across all diseases. Disease-specific instruments have been developed to detect specific disease and/or treatment-related effects. Compared to generic instruments, disease-specific instruments tend to be more responsive to small changes that are important to clinicians and/or patients.(33) The most widely used cancer-specific HRQoL instruments are the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) suite and the Functional Assessment of Cancer Therapy (FACT) questionnaire suite.(34, 35) EORTC and FACT questionnaire suites consist of a "core questionnaire" (EORTC QLQ-C30 or FACT-G), which can be supplemented by tumour-, treatment- or symptom-specific modules as required. Both questionnaire suites have been shown to be valid and reliable in older adults with cancer.(36-38) However, the EORTC QLQ is the only questionnaire suite with a supplementary module specifically developed to address issues affecting older adults with cancer.(38)

**EORTC QLQ-C30 and QLQ-ELD14**

The EORTC quality of life questionnaire (QLQ) suite is a widely used set of cancer-specific, self-administered, multidimensional questionnaires used to measure HRQoL. The EORTC QLQ-C30 was developed for a general cancer patient population and forms the core of the QLQ suite. The QLQ-C30 covers core domains of HRQoL that are relevant to patients with cancer, regardless of the site and stage of the cancer, and the demographic and treatment profile of the target patient population. The EORTC therefore mandates its use with all modules. For this study, the appropriate supplementary module is the QLQ-ELD14, as it was developed to assess age-specific HRQoL issues that affect older people (>70 years) with cancer.(38)

The QLQ-C30 is a 30-item self-reported questionnaire that consists of five functional scales (physical [PF2], role [RF2], emotional [EF], cognitive [CF] and social [CF]), three symptoms scales (fatigue, pain, and nausea/vomiting), six single-item symptom measures (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) and a two-item global health status / global QoL scale.(34) The QLQ-C30 global health status and global QoL questions are rated on a scale from 1 (very poor) to 7 (excellent). All other items on the QLQ-C30 are rated on a scale from 1 (not at all) to 4 (very much). Linear transformation is used to standardise raw scores to range between 0 and 100.(39) A higher score on a functional scale correlates with a higher ("better") level of functioning, whilst a higher score on a symptom scale correlates to a higher ("worse") level of symptoms.

The QLQ-ELD14 is a 14-item supplementary module that consists of five multi-item scales (mobility, worries about others, future worries, maintaining purpose and illness burden) and two single item measures (joint stiffness and family support). All items on the QLQ-ELD14 are rated on a scale from 1 (not at all) to 4 (very much). Linear transformation is used to standardise raw scores to range between 0 and 100.

We will use the EORTC QLQ-ELD14 in conjunction with QLQ-C30 to measure HRQoL in our study population because it is the only validated age-specific instrument for assessing HRQoL in cancer patients aged >70 years.

**EQ-5D-5L**

Multi-attribute utility instruments (MAUI) are a particular type of HRQoL instrument that have been developed using a preference-based scoring algorithm which allows derivation of quality-adjusted life years (QALY) for health economic evaluation. The EQ-5D-5L is a standardised MAUI developed by the EuroQol Group for use as a generic, preference-based measure of health outcomes.(40) It is applicable to a wide range of health conditions and treatments and provides both a compact descriptive profile and a single index value for clinical and economic evaluation. The EQ-5D-5L a relatively simple instrument, with only five items covering the 5 dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension comprises 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The questionnaire also records the respondent's self-rated health status on a vertical graduated visual analogue scale ranging from 0 (worse imaginable health state) to 100 (best imaginable health state). Responses to the 5 items can also be converted to a weighted health state index (utility score) based on values derived from general population samples. The EQ-5D is an acceptable MAUI for use in the utility valuation of health outcomes by the Australian Pharmaceutical Benefits Advisory Committee (PBAC).(41)

The EuroQol-5-Dimensions-5-Levels (EQ-5D-5L) will be used to measure HRQoL and health utilities in this study.

## 1.2.3. Rationale for use of Trial Outcome Index as the primary endpoint

HRQoL analysis usually involves reporting a range of multi-item scales, and sometimes single items, to represent the multi-dimensional aspects of HRQoL, following the scoring algorithm specified by the developer of the HRQoL instrument. However, the reporting of multiple scales as a primary endpoint involves multiple hypothesis testing which can be undesirable.(43) If multiple hypothesis testing is not accounted for, the overall type-1 error rate is inflated by the number of HRQoL scales analysed. For example, if the conventional 5% error rate is used for each of five HRQoL scales, the probability of a false positive finding across all hypotheses may be as high as 25% (if all the HRQoL scales are uncorrelated), and will certainly exceed the conventional threshold of 5%. One approach is to fix the overall type-1 error rate, typically at 5%, and to share it among multiple endpoints by downward adjustment of the type-1 error threshold for each endpoint. Another approach is to combine multiple scales and/or items into a single composite primary endpoint defined *a priori*. This latter approach is appropriate when that composite endpoint captures all of the most important anticipated effects of an intervention. We have opted for the latter approach, and have created the Trial Outcome Index (TOI) as a composite endpoint devised for this study to match aspects of HRQoL that are thought to be important to older adults with cancer. This strategy eliminates multiple hypothesis testing and should also enhance the statistical efficiency of the analysis.(44, 45) We will test this latter assumption in the psychometric evaluation sub-study (refer to **4.6.**).

The TOI consists of the linear transformation from 0 to 100 of the unweighted summed score of 12 items from the QLQ-C30 and QLQ-ELD14, covering: physical functioning (PF2; QLQ-C30 items 1-5), role functioning (RF2; QLQ-C30 items 6-7), social functioning (SF; QLQ-C30 items 26 and 27) and mobility (MO; QLQ-ELD14 items 31, 33 and 34).(34, 38) A higher score on the TOI represents better functioning. The TOI addresses a broader aspect of HRQoL than its individual component scales, and represents the physical and functional aspects of quality of life, which are fundamental indicators of the overall impact of illness and treatment on an elderly person's quality of life. Using the conceptual framework of the International Classification of Functioning, Disability and Health (ICF), the TOI measures activities (i.e. functioning at the level of the individual) and participation (i.e. functioning of a person as a member of society).(42) Therefore, the change in the TOI score of a person represents the overall impact of the physical condition or medical treatment on activities of the person and participation of the person in different areas of life.

Among the HRQoL instruments used in clinical research and practice, there is no standard procedure concerning the construction of summated scores.(46) However, a precedent for combining the physical/functional scales into a summary index is provided by the FACT questionnaires suite. The FACT Trial Outcome Index (FACT-TOI) is the sum of the 3 subscales: the Physical Wellbeing and Functional Wellbeing scales of the FACT-G and the additional concerns scale of the site or treatment specific module. The FACT-TOI has been shown to be responsive to change in physical/functional outcomes in a range of patient populations and clinical settings, sometimes even more responsive than a total (overall) multidimensional aggregated score which includes social and emotional well-being.(47) While social and emotional well-being are very important to quality of life, they are not as likely to change as quickly or dramatically over time or in response to medical therapies.

The validation study for the QLQ-ELD14 demonstrated high correlation between the four scales in the TOI.(38) Increasing the number of correlated items in a scale should increase the scale's reliability, hence precision, and thereby reduce 'noise'.(44, 45) Therefore, combining these scales into a summary index is highly likely to increase the reliability and statistical efficiency.(46, 48) The TOI should therefore provide a more powerful test of effectiveness of the intervention for any given sample size, relative to any one of its component scales. Therefore, we will use the TOI as the primary endpoint, and as part of the psychometric evaluation, assess its statistical efficiency relative to its component scales.

Claiming a statistical and meaningful improvement in HRQoL implies that: (i) all HRQoL domains that are important to interpreting change in how the clinical trial's population feels or functions as a result of the targeted disease and its treatment were measured; (ii) a general improvement was demonstrated; and (iii) no decrement was demonstrated in any domain.(32) Therefore, all the individual scales and items on the QLQ-C30, QLQ-ELD14 and EQ-5D-5L will be reported in the secondary HRQoL analyses to assist in interpretation of the primary endpoint and to provide a comprehensive assessment of the impact of the intervention on all domains of HRQoL assessed.

### 1.2.4. Rationale for psychometric evaluation of the Trial Outcome Index

Psychometric evaluation of the properties of a HRQoL instrument involves determining its reliability, validity, sensitivity, responsiveness and interpretability.(49) Reliability describes the overall consistency of an instrument and represents the extent to which a measure is free from random error. Validity refers to the extent to which evidence and theory supports whether the instrument measures what it is intended to measure, and that it is useful for its intended purpose. An instrument's sensitivity is the ability of the instrument to detect differences between patients or groups of patients that are clinically distinct. Responsiveness is similar to sensitivity but relates to the ability to detect changes when a patient improves or deteriorates. Interpretability relates to whether the observed change is important from the patient's or clinician's perspective.

Although the items in the EORTC QLQ-C30 and the QLQ-ELD14 have undergone a continual process of validation across a range of health care contexts and disease groups, and in different nationalities and cultures, combining different items of the questionnaires into the TOI is novel and therefore needs to be re-validated. Therefore, we plan to perform a psychometric evaluation of TOI in our specific study population of older adults ($\geq$70 years) with cancer receiving chemotherapy.

## 1.3. Benefit-Risk Assessment

### 1.3.1. Potential Study Benefits

The benefits of this research are potentially quite large. Specifically, this study may yield important information about the effectiveness of an integrated oncogeriatric approach on patient outcomes, which may ultimately lead to an improved clinical approach to the care of older adults with cancer. If this study holds true, it will be the first randomised controlled trial to demonstrate the effectiveness of an integrated oncogeriatric approach on key clinical outcomes in older adults with cancer.

### 1.3.2. Potential Study Risks

The risks associated with this research are comparatively small and relate to the potentially distress that may be caused by some of the items within the questionnaire.

# 2. Study Objectives

## 2.1. Aim

The aim of this prospective, randomised controlled study is to evaluate the effects of integrated geriatric care on HRQoL and other key clinical outcomes in older adults with cancer receiving chemotherapy.

## 2.2. Objectives

**Primary Objective**

- Assess the effects of integrated geriatric care on HRQoL in older adults with cancer receiving chemotherapy

**Secondary Objectives**

- Assess the effects of integrated geriatric care on survival, function, mood, nutrition, health utilities, chemotherapy delivery, healthcare utilisation and institutionalisation

**Exploratory Objectives**

- Perform a comparative economic evaluation of integrated geriatric care compared to standard oncology care
- Evaluate the interventions that result from integrated geriatric care
- Evaluate the relationship between components of HRQoL and comprehensive geriatric assessment (CGA) with clinical outcomes
- Develop a brief geriatric assessment screening tool and predictive model for older adults with cancer
- Compare the EORTC QLQ-C30 and QLQ-ELD14 with the EQ-5D-5L

**Psychometric Analysis Sub-study**

- Evaluate the relative statistical efficiency of the Trial Outcome Index (TOI) against its component scales
- Confirm the reliability and validity of the TOI in the study population
- Estimate the Minimal Important Difference (MID) for clinical significance of the TOI

# 3. Study Design and Methods

## 3.1. Study Design

The design is a prospective, open-label, randomised, controlled, parallel group, superiority study of integrated geriatric care versus standard oncology care.

## 3.2. Study Population and Setting

The study will include participants aged ≥70 years with cancer receiving chemotherapy. The study will be conducted at Eastern Health, a public health organisation in the eastern metropolitan area of Melbourne, Victoria Australia. Participants will be recruited throughout Eastern Health where oncology services are delivered, including Box Hill Hospital (a tertiary acute hospital), Maroondah Hospital (a secondary acute hospital) and Yarra Ranges Health (a community centre providing day oncology and oncology outpatient service).

### 3.2.1. Inclusion Criteria

1. Aged 70 years or older
2. Pathologically confirmed solid organ cancer or diffuse large B-cell lymphoma
3. Planned for cytotoxic chemotherapy, targeted therapy or immunotherapy
4. Able to effectively understand the language of the quality of life questionnaires in one of the validated languages for the questionnaires
5. Able to give written informed consent before randomisation according to local, national and international regulations

### 3.2.2. Exclusion Criteria

1. Have received cytotoxic chemotherapy, targeted therapy or immunotherapy within 3 months prior to enrolment
2. Unable to self-complete the HRQoL questionnaires
3. Any condition (e.g. psychological, geographical, etc.) that does not permit compliance with the protocol
4. Prior enrolment in this study

### 3.2.3. Co-enrolment Guidelines

1. Co-enrolment in other trials is permitted

## 3.3. Recruitment

Participation in the study will be completely voluntary. Potential participants will be referred by their treating clinicians to the researcher and, if interested, they will be provided with a Participant Information and Consent Form (PICF) and given sufficient time to consider whether or not to participate in the study. If they are willing to participate in the study, participants will be requested to sign the PICF and an optional Medicare Australia participant consent form. Once a participant has consented, participants will be screened for suitability according to the inclusion and exclusion criteria (refer to **3.2.1.** and **3.2.2.**). If they are suitable to participate in the study, the study doctor will perform the baseline assessment prior to treatment allocation. All participants will also receive brief generic advice about nutrition and activity and will be given the Cancer Council of Victoria's booklet on "Understanding Chemotherapy: a guide for people with cancer, their families and friends".(50) The provision of generic information prior to treatment allocation is being performed to reduce any non-specific therapeutic effect of seeing the study doctor and to encourage patients to continue with the study regardless of treatment allocation.

# 3.4. Treatment Allocation

## 3.4.1. Method of Treatment Allocation

Participants will be randomly assigned via a computerised system using the method of minimisation (with a 80:20 random element) to receive integrated geriatric care or standard oncology care in a 1:1 ratio.(51) In this study, minimisation will be used to achieve balance between groups using the following characteristics:

- treatment intent
- tumour type
- age
- gender
- ECOG performance status (physician-rated)

An 80:20 random element was determined to be the optimal value to reduce predictability whilst retaining balance.(52) This method will be conducted using the MinimPy software package by a researcher not involved in the care of the study participants.(53)

In accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT), full details of the randomisation scheme are not provided in the study protocol.(54) Knowledge of these details might undermine randomisation by facilitating deciphering of the allocation sequence. Instead, this specific information will be provided in a separate document with restricted access.

## 3.4.2. Allocation Concealment

The researcher conducting treatment allocation will be blinded to the results of all assessments and outcome measures except the variables required to allocate participants (i.e. treatment intent, tumour type, age, gender and ECOG performance status). Allocation concealment will be ensured, as the allocation code will not be released until the participant has been recruited into the study, which takes place after all baseline measurements have been completed.

# 3.5. Study Intervention

## 3.5.1. Integrated Geriatric Care

Participants assigned to the intervention arm of the study will receive integrated geriatric care, in addition to standard oncology care (refer to **3.5.2**). Integrated geriatric care consists of a comprehensive geriatric assessment and management performed by the study doctor who is a consultant physician in the specialty of Geriatric Medicine. It has two essential components: the process of assessment coupled with an appropriate management plan.

The assessment should as a minimum cover:

- current active medical problems
- past medical history
- medication review
- immunisation status
- advanced care planning arrangements
- current and previous physical functioning
- psychological functioning including cognition and mood
- social function including living arrangements, financial arrangements, community services, social support and carer issues

The PRO measures collected at baseline assessment (except for the HRQoL questionnaires) and timed-up-and-go test (TUG) will form a component of the comprehensive geriatric assessment and will be available to the study doctor. Additional components of the comprehensive geriatric assessment will be collected using an additional self-reported questionnaire (refer to **Appendix 11**). This self-reported questionnaire is based on a modification of the Adelaide Tool(14) and the Cancer and Aging Research Group's predictive model for chemotherapy toxicity(21), and includes:

- Medical Outcome Survey (MOS) Core Survey items on general health, health change, ability to walk 1 block and social activity limitation because of physical/emotional health
- MOS Social Support Survey items on tangible support (4 of 4 items) and emotional social support (1 of 8 items),
- Older Americans Resources and Services (OARS) items on hearing and vision
- number of falls in the last 6 months
- Center for Epidemiologic Studies Depression scale (CES-D) items on exhaustion
- pain numerical rating scale
- Distress Thermometer and Canadian Problem Checklist (20 of 21 items; one item on practical problems related to work/school was not included because it was thought not relevant to the study population's age-group)

The remainder of the assessment and development of the management plan must include a personal attendance by the study doctor. This attendance should include performance-based assessment of cognition by Montreal Cognitive Assessment (MoCA). A prioritised list of diagnoses/problems will be developed based on the information derived from the history and examination, and any additional information provided by other means, including an interview of a person other than the patient.

The management plan will be individualised to the patient's needs and may include:

- measures to optimise concurrent health issues
- medication recommendations
- non-medication recommendations (e.g. lifestyle changes, including exercise and diet)
- assessment of the risk of chemotherapy toxicity
- referrals to relevant existing hospital and community services (e.g. allied health services, rehabilitation services, aged care services, palliative care services)

The management plan should be explained and, if necessary, provided in written form to the patient or, where appropriate, their family or carer(s). A written report of the comprehensive geriatric assessment and management plan will be communicated back to the treating oncologist and general practitioner within a maximum of 2 weeks of the assessment via email or mail. More prompt verbal communication may be appropriate.

Participants assigned to the intervention arm will receive a comprehensive geriatric assessment and management within 3 weeks of randomisation. Participants assigned to the intervention arm will continue to see their oncologists who are the participants' primary physician for treatment of their cancer and related health conditions. Further reviews with the study doctor will occur at approximately 12 weeks and 24 weeks after randomisation. The 12 weeks and 24 weeks reviews should include performance-based assessment of functional mobility by TUG. Additional reviews with the study doctor may be scheduled as required depending on medical needs.

Assessments of outcome measures occur at 12 weeks, 18 weeks and 24 weeks following randomisation. After 24 weeks, participants in the intervention arm may continue to receive integrated geriatric care but will not be required to complete further study assessments.

### 3.5.2. Standard Oncology Care

Participants assigned to the control arm will receive standard oncology care provided by their oncologist and will not have any further contact with the study doctor following randomisation. The treating clinicians will be blinded to the results of any study assessments. Assessments of outcome measures occur at 12 weeks, 18 weeks and 24 weeks following randomisation. After 24 weeks, participants will no longer be required to complete further study assessments. Although participants in the control arm may be referred to a geriatrician at any time by their treating clinicians, they will not be permitted to cross-over to receive the study-specific comprehensive geriatric assessment and management.

## 3.6. Data Collection

### 3.6.1. Required Forms

The types of data and frequency of their collection are described in the table below. Patient-reported outcome (PRO) measures will be used to assess a range of outcomes, including HRQoL by the EORTC QLQ-C30, QLQ-ELD14; function by self-rated performance status (ECOG, Karnofsky) and daily activities (ADL, IADL); mood by PHQ-9 and GAD-6; nutrition by self-MNA; and social situation. Additional data will be collected by the researcher, including participant demographics, medical history data (including comorbidities as measured by the Charlson Comorbidity Index), medications, level of care, physician-assessed performance status by ECOG and Karnofsky (KPS), CHSA Clinical Frailty Scale and Timed-Up-and-Go test (TUG). End of study data will be collected and will include a summary of participant's care whilst participating on the study and survival status.

| Required Forms | | | Week | | |
|---|---|---|---|---|---|
| | Baseline | 1 | 12 | 18 | 24 / End of Study |
| **PARTICIPANT FORMS** | | | | | |
| Participant Information and Consent Form | X | | | | |
| Medicare Participant Consent Form (optional) | X | | | | |
| Global Rating of Change | | * | X | X | X |
| EORTC QLQ-C30 v3.0 and QLQ-ELD14 | X | | X | | X |
| EQ-5D-5L | X | | X | X | X |
| TOI | | * | | X | |
| Function – ECOG, KPS, ADL, IADL | X | | X | | X |
| Mood – PHQ-9 and GAD-7 | X | | X | | X |
| Nutrition – self-MNA and G8 Screening Tool | X | | X | | X |
| Social situation | X | | X | | X |
| **RESEARCHER FORMS** | | | | | |
| Demographics | X | | | | |
| Medical History (including Charlson Comorbidity Index) | X | | | | |
| Concurrent medications | X | | X | | X |
| TUG | X | | | | |
| Physician-rated ECOG and KPS | X | | | | |
| CHSA Clinical Frailty Scale | X | | | | |
| Flemish Triage Risk Screening Tool (fTRST) | X | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Level of care | X | | X | | X |
| Height | X | | | | |
| Weight | X | | X | | X |
| Blood test results (FBE, UEC) | X | | | | |
| Chemotherapy treatment | | | X | | X |
| Healthcare utilisation | | | X | | X |
| CoMiDa Form | X | X | X | X | X |

* Performed only if participant is commencing chemotherapy on day 8 or later

### 3.6.2. Time Window for Patient-Reported Outcome and Clinical Assessments

It is very important that the PRO assessments are completed within acceptable time limits surrounding the scheduled assessments.

Baseline assessment should be completed at enrolment and must be completed prior to randomisation. The time window for baseline assessment is therefore the time between obtaining consent and treatment allocation.

For the test-retest assessment (week 1), the time window is from 7 days post-baseline assessment to immediately prior to receiving the first dose of chemotherapy.

For the follow-up assessments (week 12, week 18, week 24) and end of study assessment, a time window of up to +/- 3 weeks is allowed

Researcher forms should be completed on the same day as the PRO forms where possible.

### 3.6.3. Patient-Reported Outcome Assessments

The EORTC QLQ-C30, QLQ-ED14, EQ-5D-5L, self-rated ECOG, self-rated KPS, Katz ADL, OARS IADL, self-MNA, PHQ-9 and GAD-7 are self-administered questionnaires and are to be completed by the participant without the assistance of the site personnel. These questionnaires are to be completed using pen and paper. All questionnaires should be completed before any other study procedures are conducted.

### 3.6.4. Estimated Time Required for Patient-Reported Outcome Measures

| Assessment | Items | Time to administer (min) | Mode of Administration |
|---|---|---|---|
| Global Rating of Change | 1 | 0.5 | Self |
| EORTC QLQ-C30 v3.0 | 30 | 5 | Self |
| EORTC QLQ-ELD14 | 14 | 3 | Self |
| EQ-5D-5L | 6 | 1 | Self |
| Self-rated ECOG and self-rated KPS | 2 | 0.5 | Self |
| Katz ADL and OARS IADL | 2 | 0.5 | Self |
| Self-MNA | 5 | 1 | Self |
| PHQ-9 and GAD-7 | 16 | 3 | Self |

* Time to administer for patient-reported outcome (PRO) measures is based on using an estimate of 10 seconds per item.
** Time to administer PRO measures at each assessment timepoint will be detailed in **3.6.5.**

## 3.6.5. Study Procedure

### 3.6.5.1. Screening (Days -28 to -1)

During this visit, the participant will be thoroughly informed about all aspects of the study, including all scheduled visits and activities, in accordance with applicable ICH guidelines and local and regulatory requirements. Participant eligibility will be assessed and confirmed by the investigator. All the inclusion and exclusion criteria must be met and none of the exclusion criteria may apply. Participants must sign and date the participant informed consent form and optional Medicare Australia participant consent form **prior** to performance of any study specific procedures. The original signed and dated informed consent form(s) must be retained by the investigator in the participant's file and a copy must be provided to the participant.

### 3.6.5.2. Study Day 0 (Baseline Assessment)

Day 0 is defined as the day of enrolment and administration of baseline assessment. Study participants must sign the informed consent form and complete baseline assessment to be considered enrolled into the study. At the baseline assessment, participants complete a series of PRO measures (see **3.6.1.**) and the timed-up-and-go test (TUG) (refer to **Appendix 12A**). The time required to complete the PRO measures at baseline assessment is approximately 13 minutes. The time required to complete the TUG is approximately 2 minutes.

The researcher will also collect additional data regarding participant characteristics, disease characteristics, comorbidities and medications (see **3.6.1.**).

Treatment allocation will occur after the informed consent form and baseline assessment has been completed. For participants assigned to the intervention arm, the results of the baseline assessment (except the HRQoL questionnaires because it will be used to calculate the primary outcome measure) will be made available to the treating clinicians. For participants assigned to the control arm, treating clinicians will be blinded to the results of the baseline assessment.

### 3.6.5.3. Study Day 7 (Test-retest Assessment)

Following administration of baseline assessment, participants who are expected to commence chemotherapy on day 8 or later will be asked to self-complete a test-retest assessment on day 7 at home and post it back in the provided reply paid envelope. Participants who commence chemotherapy prior to day 8 are excluded from the test-retest assessment because this assessment requires participants to have stable HRQoL between the first and second assessment, and commencement of chemotherapy may lead to change in HRQoL. The researcher will phone the participants on day 7 to provide a reminder to complete the test-retest assessment.

The test-retest assessment consists of the Global Rating of Change (1 item) and the TOI (12 items). Estimated completion time for the 13 items in the test-retest assessment is 2 minutes.

### 3.6.5.4. Study Week 12, Week 18 and Week 24 (follow-up assessments)

Follow-up assessments are evaluated at 12 weeks, 18 weeks and 24 weeks after randomisation. Assessments are permitted within the 3 weeks period prior or 3 weeks period following the assessment time-point, with preference for assessment to be done immediately before a specified treatment cycle where possible. To avoid more frequent clinic visits, the researcher will make an effort to meet with participants at their regularly scheduled visits, such as appointments with their oncologists and chemotherapy or radiotherapy sessions. At the scheduled assessment timepoints, all participants will be asked to complete a series of PRO measures (see **3.6.1.**). The times required to complete the PRO measures at week 12 is approximately 13 minutes; week 18 is approximately 3 minutes; and week 24 is approximately 13 minutes.

The researcher will also collect additional data regarding participant characteristics, disease characteristics, comorbidities, medications, chemotherapy delivery, healthcare utilisation, level of care and survival (see **Section 3.6.1.**).

For participants assigned to the intervention arm, the results of the follow-up assessments (except for the HRQoL questionnaires) will be made available to the treating clinicians. For participants assigned to the control arm, treating clinicians will be blinded to the results of the follow-up assessments.

### 3.6.5.5. End of Study Assessment

After completion of the final scheduled follow-up assessment at week 24, participants will no longer be asked to complete any further assessments. Participants assigned to the intervention arm may continue to receive integrated geriatric care. Participants assigned to the control arm may be referred to a geriatrician at any time but they will not be permitted to cross-over to receive the study-specific comprehensive geriatric assessment and management.

If a participant discontinues from participation in the study prior to 24 weeks, they will be offered the option to complete an end of study assessment at the time of discontinuation. The end of study assessment consists of a series of PRO measures (see **3.6.1.**) which will take approximately 13 minutes to complete. If the participant is not willing or able to complete this full set of PRO measures, they will be encouraged to complete a brief assessment consisting of the TOI (12 items) and Global Rating of Change (1 item) which will take approximately 2 minutes to complete. This design is motivated by the importance of information about participants who discontinue early. Such information underpins the scientific rigour of the study analysis and reporting, as it will be used to assess the extent of potential bias due to subsequent missing data (i.e. planned assessments not completed) for these participants.

### 3.6.5.6. Long-term Follow-up for Survival

All participants will be followed up for survival status at 12 weekly intervals from the end of study visit until death, loss to follow-up or withdrawal of consent. The participant's survival status may be obtained from review of participant's medical record. If review of the participant's medical record is insufficient to determine their survival status, this information may be obtained via a telephone call to the participant, their oncologist or their general practitioner. Participants will not be required to attend any study-specific visits for follow-up.

### 3.6.6. Reporting Requirements for Missing Data

In addition to protocol-specific assessments completed by participants, the researcher will complete a compliance form for each scheduled assessment – the INTEGERATE Completion and Missing Data (CoMiDa) form (see **Appendix 13**). This form will document whether the assessments were completed and the circumstances in which they were completed. If a study participant does not complete a questionnaire, the researcher will document the reason for non-completion on the CoMiDa form. The information on missing data will be used in two ways. First, during study implementation, the information on missing data will be used to monitor rates and reasons for missing PRO data in real time to allow remedial intervention to correct administrative oversights and errors in PRO questionnaire administration. Second, the information on missing data will be used in the analysis to describe missing data patterns and to explain variability in outcomes.

Some sources of missing data cannot be avoided, such as attrition due to death and withdrawal due to progressive disease and toxicity. Other sources of missing data are considered avoidable and may be due to administrative oversights and errors in PRO questionnaire administration. Accurate records of both avoidable and unavoidable sources of missing data will be documented using the CoMiDa form.

The following approaches will be used to minimise avoidable missing PRO data: 1) PRO assessments should be administered on schedule and within allowable time windows; 2) the circumstances related to late or non-completion will be monitored (via the CoMiDa Form); and intervention should be taken to correct administrative oversights and errors in PRO questionnaire administration.

In particular, if an assessment or part of an assessment is missed, an attempt should be made to contact the participant to complete the assessment. Where possible, the participant should complete the assessments in person. If this is not possible, the questionnaire may be mailed to them with a reply paid envelope. Up to three reminder telephone calls will be made by the researcher to encourage the participant to complete and return the questionnaires by post.

## 3.7. Study endpoints

### 3.7.1. Summary of Endpoints

The primary and secondary endpoints are summarised in the table below. The primary endpoint of this study is health-related quality of life (HRQoL). The secondary endpoints are survival, function, mood, nutrition, chemotherapy delivery and healthcare and aged care service utilisation.

| Primary Endpoint | Measures |
|---|---|
| **Trial Outcome Index** | The Trial Outcome Index (TOI) consists of the linear transformation from 0-100 of the unweighted summed score of the physical functioning (PF2), role functioning (RF2) and social functioning (SF) scales of EORTC QLQ-C30, with the mobility (MO) scale of the QLQ-ELD14.<br><br>TOI = PF2 [QLQ-C30] + RF2 [QLQ-C30] + SF [QLQ-C30] + MO [QLQ-ELD14]<br><br>The individual scales on the QLQ-C30, QLQ-ELD14 and EQ-5D-5L will be reported in the secondary and tertiary HRQoL analyses to assist in interpretation of the primary endpoint. |
| **Secondary Endpoints** | **Measures** |
| **Function** | • ECOG performance status (self-reported)<br>• Karnofsky performance status (self-reported)<br>• Katz ADL scale<br>• OARS IADL scale |

| | |
|---|---|
| **Survival** | • Overall survival |
| **Mood** | • PHQ -9<br>• GAD-7 |
| **Nutrition** | • Self-MNA |
| **Health Utilities** | • EQ-5D-5L |
| **Chemotherapy delivery** | • Initial dose (standard or reduced dose; dose adjustments due to CGA)<br>• Subsequent dose (dose delay or dose reduction, discontinuation of chemotherapy due to toxicity) |
| **Healthcare utilisation** | • Hospitalisation (number, type, length of hospital stay, reason)<br>• Emergency department visits (number, reason)<br>• Referrals (type, date referred, date seen)<br>• Medical consultations<br>• Type of Pharmaceutical Benefit Scheme (PBS)-listed medications |
| **Institutionalisation** | • Social situation<br>• Level of care |

## 3.7.2. Primary Endpoint

The primary objective of this study is to assess the effects of integrated geriatric care on HRQoL in older adults (>70 years) with cancer receiving chemotherapy. The EORTC QLQ-C30 version 3.0, QLQ-ELD14 and EQ-5D-5L will be used to measure HRQoL (see **Section 1.2.2**).

The primary endpoint of this study is the TOI score (see **Section 1.2.3***).* The TOI consists of the linear transformation from 0 to 100 of the unweighted summed score of 12 items from the QLQ-C30 and QLQ-ELD14, covering: physical functioning (PF2; QLQ-C30 items 1-5), role functioning (RF2; QLQ-C30 items 6-7), social functioning (SF; QLQ-C30 items 26 and 27) and mobility (MO; QLQ-ELD14 items 31, 33 and 34). A higher score on the TOI represents higher ("better") functioning. The individual scales on the QLQ-C30, QLQ-ELD14 and EQ-5D-5L will be reported in the tertiary HRQoL analyses to assist in interpretation of the primary endpoint and to provide a comprehensive assessment of the impact of the intervention on all domains of HRQoL assessed. Note that most of these scales contain multiple items (multi-item scales), whilst the remainder contain only one item (but are still called scales). Following convention, we will not report or analyse separately any items that are aggregated into multi-item scales.

## 3.7.3. Secondary Endpoints

### 3.7.3.1. Overall Survival

Overall survival is defined as the time from randomisation until death due to any cause. Participants who are alive (including lost to follow-up) at the time of the analysis will be censored at the date when they were last known to be alive. Overall survival is a secondary endpoint of this study and will be compared between treatment arms in the following pre-specified study groups: (1) palliative-intent treatment subgroup; (2) overall study population; and (3) adjuvant/curative-intent treatment subgroup.

### 3.7.3.2. Performance status

Performance status is used to assess functional performance in cancer patients and is part of routine oncology care. Performance status is a powerful predictor of HRQoL and survival and is an important concern in cancer patients. ECOG and KPS are both widely used methods of assessing performance status of cancer patients. Self-rated ECOG and KPS score will be used to describe the performance status of the study population.

The ECOG score is a single item rating of the degree to which the patient is able to participate in typical activities without a need for rest. The scale ranges from 0 (fully active) to 5 (dead) (55) The KPS score is a single item rating of three dimensions of functional status: activity, work and self-care.(56) The KPS is an 11-point rating scale that ranges from 0 (dead) to 100 (normal functioning).

The mean self-rated ECOG score and KPS score of patients at 12 weeks and 24 weeks are secondary endpoints; they will be compared between treatment arms.

### 3.7.3.3. Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL)

In geriatric medicine, ADL and IADL is used to assess functional status and is part of routine geriatric assessment.(13) Decline in functional status is associated with adverse health outcomes such as mortality and residential care placement for older hospitalised patients. Self-reported Katz ADL scale and OARS IADL scale will be used to describe the functioning level in of the study population.(57, 58)

Katz ADL scale assesses adequacy of performance in basic activities of daily living: bathing, dressing, toileting, transferring, continence, and feeding. Each item are scored yes/no for independence in each of the six functions. A summary score ranges from 0 (unable to perform any activity) to 6 (able to perform all activities).

OARS IADL is an easy to administer assessment instrument that provides self-reported information about functional skills necessary for independent living in the community. These skills are considered more complex than the basic activities of daily living as measured by the Katz ADL scale. The 7-items on the OARS IADL assesses the following domains of function: telephone, shopping, food preparation, housekeeping, mode of transportation, medications and finances. Each item is scored on a 3-point Likert-like scale, with the total score ranging from 0 (unable to perform any activity) to 14 (able to perform all activities).

Disability in ADL and IADL is defined as the need for assistance to complete at least one ADL or IADL, respectively. Functional decline in ADL and IADL is defined as any decrease in ADL and/or IADL score between baseline and follow-up assessments.

The proportion of participants in each treatment arm with functional decline in the ADL and/or IADL scores at 12 weeks and 24 weeks are secondary endpoints of this study; they will be compared between treatment arms.

#### 3.7.3.4. Mood

Anxiety and depression are common symptoms in patients with advanced cancer. Integrated geriatric care may alleviate some of these symptoms by provided additional support and reducing social isolation.

PHQ-9 and GAD-7 will be used to measure the prevalence of depression and anxiety in the study population. PHQ-9 and GAD-7 are subscales of the Patient Health Questionnaire, a patient self-rated version of the Primary Care Evaluation of Mental Disorders which is a widely used screening tool for mental health disorders in primary care.(59)

The PHQ-9 is a brief, self-rated questionnaire that was developed to screen for depression. It has 9-items derived from the Diagnostic and Statistical Manual of Mental Disorders, 4$^{th}$ Edition, Text Revision (DSM-IV-TR) criteria for major depressive disorder.(60) For each item the participant is asked to rate how much over the 2 weeks they have been bothered by the symptoms. Scoring is on a Likert-type scale from 0 to 3 (0 indicates not at all; 1 indicates several days; 2 indicates more than half the days; 3 indicates nearly every day). The PHQ-9 scored as a continuous measure has good discriminating power between cases and non-cases of major depressive disorder in cancer outpatients, with an area under the curve (AUC) of 0.94 (95% confidence interval [CI], 0.93-0.95) on ROC analysis.(61)

The GAD-7 is a brief, self-rated questionnaire which was originally developed as a screen for Generalised Anxiety Disorder (GAD), and is frequently used in conjunction with the PHQ-9.(62) Scoring of its 7-item is on a Likert-type scale from 0 to 3 (0 indicates not at all; 1 indicates several days; 2 indicates more than half the days; 3 indicates nearly every day). Anxiety in cancer is thought to be most closely related to the free floating anxiety characteristic of GAD.(63). The GAD-7 is gaining use in screening for a range of anxiety disorders due to its brevity and good psychometric properties.

An estimate of clinical important levels of depression and anxiety can be made using cut-off scores for PHQ-9 and GAD-7. Scores of 5, 10, 15 represent cutpoints for mild, moderate, and severe levels of depression and anxiety, on the PHQ-9 and GAD-7 respectively.(62) A recommended cutpoint for further evaluation and treatment is a score of 10 or more on both measures.(62) A score of 9 or less requires no action or monitoring.

The proportion of participants in each of the PHQ-9 and GAD-7 categories in the two treatment arms at 12 weeks and 24 weeks are secondary endpoints of this study; they will be compared between treatment arms.

#### 3.7.3.5. Nutrition

The self-MNA will be used to describe the nutritional status in the study population. The MNA is a nutritional screening instrument which was especially developed and validated for use in the elderly.(64) The fully validated self-completed version of the MNA (self-MNA) consists of 6-items which are scored between 0 and 14. (65) The self-MNA takes 3 minutes to complete and is as effective as the full MNA to identify malnutrition.(65) A full MNA score of $\leq$23.5 has been shown in to be a predictor of early death in older adults treated with first-line chemotherapy for cancer.(66) A self-MNA score of $\leq$11 points is considered to be equivalent to a full MNA score of $\leq$23.5.

The proportion of participants with self-MNA score $\leq$11 points and >11 points in the two treatment arms at 12 weeks and 24 weeks is a secondary endpoint of this study and will be compared between treatment arms.

#### 3.7.3.6. Health Utilities

The EQ-5D-5L will be used to describe the health utilities in the study population and as part of the health economic analysis. See **Section 1.2.2.** for a full description of this instrument.

The EQ-5D-5L health utility score in the two treatment arms at 12 weeks and 24 weeks are secondary endpoints of this study and will be compared between treatment arms.

#### 3.7.3.7. Chemotherapy Delivery

Chemotherapy delivery will be assessed over the 24 weeks period from start of chemotherapy by dose intensity, dose reduction and treatment delays. Relative dose intensity (RDI) will be calculated based on the ratio of delivered dose intensity of chemotherapy to standard dose for the time period.

Secondary endpoints of this study are the mean RDI of chemotherapy, the proportion of participants with dose reduction $\geq$10% from previous dose and the proportion of participants with treatment delays of more than 14 days in the two treatment arms at 12 weeks and 24 weeks; they will be compared between treatment arms.

#### 3.7.3.8. Healthcare Utilisation

Healthcare utilisation is an important consideration in healthcare service delivery. By improving support to participants, integrated geriatric care may potentially reduce the rate of emergency department visit, unplanned hospital admissions and length of hospital stay. Data on cause and duration of any emergency department visits or hospital admissions during the study period will be extracted from participant's hospital record.

Secondary endpoints of this study are the mean number of: emergency department visits, hospital admissions (including length of hospital stay; and divided into planned and unplanned), medical consultations and type of PBS-listed medications in the two treatment arms from randomisation to 12 weeks and 24 weeks post-randomisation; they will be compared between treatment arms. An additional secondary endpoint is the hazard ratio for hospitalisation of participants in the two treatment arms; this will be compared between treatment arms.

#### 3.7.3.9. Institutionalisation

Social situation and level of care will be used to determine institutionalisation in the study population. Social situation differentiates between living at home alone, home with others or residential care. Level of care is determined by the Aged Care Assessment Service (ACAS) and differentiates between independent, low level care and high level care. For participants who are admitted to hospital, rehabilitation facility or palliative care facility at the time of assessment, the social situation and level of care is considered to be the discharge destination and level of care on discharge, respectively. Institutionalisation is defined in this study as residing in a residential aged care facility.

A secondary endpoint of this study is the hazard ratio of institutionalisation of participants in the two treatment arms; this will be compared between treatment arms. In addition, the level of care level of care and social situation will also be described in the treatment arms.

# 4. Statistical Procedures

## 4.1. Overview

All analyses will be conducted as defined in a formal statistical analysis plan (SAP) for the analysis and presentation of data. The SAP will be finalised prior to commencement of study analysis and approved by the Trial Management Committee (TMC).

All analyses will be conducted according to the intention-to-treat principle: all eligible and evaluable participants will be included in the analysis and analysed according to the arm randomised to (using the as-randomised participant population).

Baseline characteristics by treatment arm will be summarised in frequency tables and by use of descriptive statistics for quantitative variables. Summary tables will be prepared giving numbers of participants by treatment arm and by randomisation irregularities, treatment compliance, eligibility infringements, and losses to follow-up (as per CONSORT guidelines).(67)

## 4.2. Sample size requirement

Based on reviews of published studies, a minimal important difference (MID) in patient-reported outcome (PRO) scores has commonly been set at approximately half the standard deviation; that is, equivalent to an effect size of 0.50.(68, 69) An effect size of 0.5 is commonly regarded as a medium difference and a meta-analysis has shown it to be clinically relevant in studies of HRQoL using QLQ-C30 as an outcome measure.(70, 71) The target sample for this study is based on an independent t-test at a 2-sided significance level of 0.05 to have an 80% power to test the null hypothesis of no true between-group difference in the change in the TOI score from baseline to 12 weeks, versus the alternative hypothesis of a difference, with an effect size of 0.5. Under these assumptions, a minimum sample size of 64 evaluable participants in each group (or a total of approximately 128 evaluable participants) who have completed the HRQoL questionnaires at baseline and 12 weeks is required.

## 4.3. Primary Efficacy Analysis: HRQoL

### 4.3.1. Overview

The primary efficacy analysis will address the primary objective of this study which is to assess the effects of integrated geriatric care on HRQoL in older adults with cancer receiving chemotherapy. This will involve a hierarchical set of HRQoL analyses, described below as the primary, secondary and tertiary HRQoL analyses.

The primary HRQoL analysis will relate to the primary endpoint of the study, the TOI, which represents the subset of HRQoL domains most likely affected by the study intervention. The primary HRQoL analysis will employ linear mixed models, with pattern-mixture models and/or joint model of longitudinal and survival data as sensitivity analyses. The secondary HRQoL analyses will also relate to the TOI and compare: i) the proportions of participants who experience change in TOI by at least the clinically important threshold, using Fisher's test; and ii) time to change in TOI by at least the clinically important threshold using log-rank test. Finally, the tertiary HRQoL analyses involve analyses of all the scales of the EORTC QLQ-C30, QLQ-ELD14 and EQ-5D-5L using t-test or Wilcoxon test (according to normality of distribution), to complement the primary and secondary HRQoL analyses, to make full use of all HRQoL data collected and to assist in interpretation of the of the primary endpoint.

## 4.3.2. Missing HRQoL data patterns

Prior to conducting analyses of HRQoL data, rates and reasons for missing PRO questionnaires will be summarised to assess the extent to which data are missing at random. This is an important first step, as it aids interpretation of the results of HRQoL outcome analyses relative to the assumptions of those analyses.

A table of PRO completion rates by arm will be reported. Following NCIC Clinical Trials Group (NCIC CTG) recommendations(72), completion rates at each follow-up timepoint will be calculated in two ways, that is, PRO assessments completed as a percentage of: 1) all participants recruited (i.e. number of baseline PRO completions); 2) number of PRO assessment expected (i.e. number of participants still alive and on-study at that timepoint).

To explore mechanisms of missingness, a graph of the TOI versus time will be graphed, stratified by dropout time.(73) If the trajectories over time are substantially different, this will suggest data are not missing completely at random. For example, if participants who have lower baseline values are more likely to drop out, or if steeper rates of decrease in TOI over time are associated with earlier dropout, missing data are more likely to be linked with sicker participants. We will also use these graphs to assess whether the separation between the missingness patterns is more dramatic in the intervention arm than the control arm.

## 4.3.3. Primary HRQoL Analysis

The primary HRQoL analysis is defined prospectively as a comparison of the longitudinal change in TOI scores for significant between-group difference using linear mixed models. The models will include baseline variables (baseline TOI score, and possibly other baseline variables predictive of TOI outcome) as covariates and treatment arm and time (and their interaction) as fixed effects. Time will include the baseline, 12 week, 18 week and 24 week time-points.

These models account for covariance between repeated measures on participants and will be used to: i) describe the time course of the TOI over time; ii) assess whether the time course differs between the two treatment arms by testing the study arm-by-time interaction; and iii) estimate and test differences between the two treatment arms at specific time points of interest via selected linear contrasts. Sensitivity analyses will be performed using pattern-mixture models and/or joint model of longitudinal and survival data to help interpret results if greater than 20% of the TOI data are missing, and if reasons for missing data (from the CoMiDa form) and patterns of missing data (described in **Section 4.3.2**.) suggest that these when data are not missing at random.

### 4.3.3.1. Subgroup Analysis for the Primary Efficacy Endpoint

In addition to the analysis of the overall study population, pre-specified subgroup analysis will be conducted for the TOI (primary efficacy endpoint) using linear mixed models to detect significant differences in longitudinal change in TOI score between treatment groups in the following subgroups: i) palliative-intent treatment subgroup; and ii) adjuvant/curative-intent treatment subgroup.

### 4.3.4. Secondary HRQoL Analyses

Secondary HRQoL analyses, defined prospectively, includes: i) comparison of the proportions of participants in the two treatment arms with at least 10 units deterioration in TOI score at 12 weeks and 24 weeks by using Fisher's exact test (as recommended by NCIC CTG)(72); and ii) time to deterioration in TOI score (defined as the time from randomisation to a minimum 10 units deterioration in change score from baseline) by log-rank test.

### 4.3.5. Tertiary HRQoL Analyses

Tertiary HRQoL analyses will be performed on all scales of the EORTC QLQ-C30, QLQ-ELD14 and EQ-5D-5L to complement primary and secondary HRQoL analyses, to make full use of all HRQoL data collected, and to assist in interpretation of the primary endpoint. The t-test or Wilcoxon test will be applied, depending on normality of distribution, to each of the scales of the QLQ-C30 and QLQ-ELD14 (using the EORTC's standard scoring algorithms) and the EQ-5D-5L, to assess between-group differences in change from baseline to 12 weeks and 24 weeks, across a comprehensive range of HRQoL domains. The TOI will also be analysed in this way for completeness.

### 4.3.6. Adjustment for Multiple Hypothesis Testing

For the primary HRQoL analysis, adjustment for multiple comparisons of TOI differences at specific times will be undertaken using the Hochberg method.(74) No formal adjustment will be used for other secondary or exploratory analyses. In general, two-sided P-values will be used and 95% confidence limits for all important endpoints will be reported.

## 4.4. Secondary Efficacy Analyses

### 4.4.1. Overall Survival

Overall survival between treatment groups will be analysed using a closed hierarchical method in the following pre-specified order: (1) palliative-intent treatment subgroup; (2) overall study population; and (3) adjuvant/curative-intent treatment subgroup.

Overall survival will be estimated using the non-parametric Kaplan-Meier method. Summary statistics will be presented with appropriate confidence intervals. The non-parametric log rank test will be used to compare the two arms of the study and, if appropriate, a Cox proportional hazard model will be used to estimate the treatment effects. Additional details will be provided in the SAP.

### 4.4.2. Other Secondary Endpoints

Other secondary endpoints will be summarised according to established guidelines specific to the measurement instrument. In general, categorical variables will be tabulated and key summary statistics (mean, standard deviation, median, range, etc.) will be presented for continuous measurements. Comparisons between treatment arms will be made where appropriate and the test selected depending on the distribution. Additional details will be provided in the SAP.

## 4.5. Exploratory Analyses

### 4.5.1. Economic Evaluation

An exploratory economic evaluation will be performed comparing the healthcare costs and benefits of integrated geriatric care compared to standard oncology care from randomisation to 24 weeks post-randomisation. Data on outcomes will be collected on study participants including health utilities through the EQ-5D-5L and costs will be calculated for the use of healthcare resources such as Medicare-reimbursed costs, medications (including chemotherapy), emergency department visits, hospital stays and the use of other healthcare services (including allied health, rehabilitation, aged care and palliative care).

Health economic data will be assessed using descriptive statistics. Healthcare utilisation will be valued using standard hospital and/or Medicare prices to obtain total cost per participant. The Incremental Cost-Effectiveness Ratio (ICER) will be calculated as the cost per adjusted quality adjusted survival (cost/QALY gain), using the EQ-5D-5L utility scores. The robustness and validity of these results will be tested using sensitivity analyses.

### 4.5.2. Interventions that result from integrated geriatric care

An exploratory objective of this study is to evaluate the interventions that result from integrated geriatric care. Data on medication prescribing patterns, recommendations made, referral patterns and adherence to recommendations will be collected on the study participants. Comparisons between treatment arms will be made where appropriate and the test selected depending on the distribution.

### 4.5.3. Relationship between components of HRQoL and CGA with clinical outcomes

An exploratory objective of this study is to assess which components of HRQoL and CGA predict clinical outcomes. The relationship between HRQoL and CGA components with survival, functional decline, chemotherapy delivery and healthcare utilisation will be evaluated. Specifically, the self-MNA, G8 screening tool, Flemish version of the Triage Risk Screening Tool (fTRST), CHSA clinical frailty scale, Adelaide Tool's assessment of frailty, Balducci criteria for frailty and the Cancer and Aging Research Group's model for predicting chemotherapy toxicity will be evaluated in terms of their ability to predict clinical outcomes.(14, 21, 28, 65, 75, 76)

### 4.5.4. Development of a brief geriatric assessment screening tool and predictive model for older adults with cancer

An exploratory objective of this study is to develop a brief geriatric assessment screening tool to detect health-related issues in older adults with cancer and to develop a predictive model to detect older adults with cancer who are at risk of poor clinical outcomes.

First, shorter versions of existing screening instruments will be compared against the full version. Specifically, the PHQ-4 will be compared against PHQ-9 and GAD-7 as a screening instrument for symptoms of depression and anxiety in the study population. PHQ-4 consist of the first two items of the PHQ-9 and GAD-7, and constitute the two core DSM-IV items for major depressive disorder and generalised anxiety disorder, respectively.(77, 78)

Next, in order to determine the effectiveness of different CGA components in screening for problems, comparisons will be made between different CGA components (e.g. 20-item problem checklist) and interventions that result from integrated geriatric care.

In addition, consideration will be given to developing a predictive model for clinical outcomes in older adults with cancer using a multivariate logistic regression model or cluster analysis.

### 4.5.5. Comparison of EORTC QLQ-C30 and QLQ-ELD14 with EQ-5D-5L

An exploratory objective of this study is to compare the outcomes produced by the QLQ-C30 with the EQ-5D-5L. Two approaches will be taken. One approach will use regression methods to map the scales and items of the EORTC QLQ-C30 and QLQ-ELD14 to the health-utility scores of the EQ-5D-5L(79) This approach has been applied to a range of cancer patient populations, but has not yet been applied to an elderly cancer population, nor has the QLQ-ELD14 been mapped to a utility score. This analysis will provide insights into which domains of HRQoL that contribute most to health utility for elderly cancer patients. The other approach will use an algorithm to directly convert participant's QLQ-C30 responses into a utility score using Australian general population utility weights.(80) The resultant QLQ-C30-based utility scores will be compared with the EQ-5D-5L utility scores in terms of their responsiveness to changes in HRQoL and statistical efficiency (using the same analyses to compare the TOI with its component scores as described in **Section 4.6**).

## 4.6. Psychometric Evaluation Sub-Study Analysis

Standard psychometric analyses will be employed to evaluate the properties of the TOI in the study population with regards to its reliability, validity, sensitivity, responsiveness and the minimal important difference (MID). In addition, the relative statistical efficiency of the TOI will be compared with its component scales. Additional details will be provided in the SAP.

# 5. STUDY STRUCTURE

## 5.1. Trial Management Committee

The study will be overseen by a Trial Management Committee (TMC). The TMC responsibilities include protocol development, study planning, monitoring of progress and participant safety, review of information from related research and implementation of recommendations from other study committees and external bodies, and publication.

# 6. ETHICAL CONSIDERATIONS AND GENERAL STUDY ADMINISTRATION

## 6.1. Ethical and Regulatory Compliance

This study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans (Commonwealth of Australia 2001) and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2004. The investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a subject.

## 6.2. Ethics Committee

This protocol, the informed consent forms and relevant supporting information must be submitted to the relevant Independent Ethics Committee (IEC) and reviewed and approved by the IEC before the study is initiated.

## 6.3. Confidentiality

This study will be conducted in accordance with applicable Privacy Acts and Regulations. The investigator will ensure that the participant's anonymity is maintained. Participants will not be identified in any publicly released reports of this study. All records will be kept confidential to the extent provided by Commonwealth, state and local law. All study-related information will be stored securely in areas with limited access and will only be available to staff directly involved with the study. All electronic data will be secured with password-protected access systems. All records that contain names or other personal identifiers, such as informed consent forms, will be stored separately from study records identified by code number. Each participant enrolled will be assigned a unique participant identification number. This means that participant names are not included in data sets that are submitted for analysis. The investigator will keep a participant enrolment log showing codes, names and addresses in a secure file separate from study records.

Participant medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the informed consent form (or separate authorisation for use and disclosure of personal health information) signed by the participant, unless permitted or required by law. Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purpose.

## 6.4. Study Registration

This study has been registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) on 14 April 2014 and allocated the registration number: ACTRN12614000399695.

## 6.5. Protocol Amendments

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the participant or may affect participant safety, including changes of study objectives, study design, participant population, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Approval must be obtained from the TMC and IEC before implementation of any changes, except for changes necessary to eliminate any immediate hazard to a subject or changes that involve logistical or administrative aspects only (e.g. change in contact information).

## 6.6. Study Termination

Although there is every intention of completing the study, the TMC reserves the right to discontinue the study at any time for clinical or administrative reasons. In terminating the study, the TMC will assure adequate consideration is given to the protection of the participants' interests. Reasons for terminating the study may include:

- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of participants

## 6.7. Data Handling and Record Keeping

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, informed consent forms and documentation of IEC approval.

Study data will be collected on the case report forms (CRF) designed for the study or an electronic data system. The investigator is responsible for assuring that the data collected is complete, accurate, and recorded in a timely manner. Data for CRFs will be collected during participant visits, phone calls with participants and health care providers, participant diaries and abstracted from the medical record.

## 6.8. Publication of Data

Results of this study may be published in peer-reviewed journal(s), presented at seminars and scientific meetings, and will form part of a doctoral thesis. Publications and presentations of any results from this study shall be in accordance to accepted scientific practice, academic standards and custom.

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# INTEGERATE PROTOCOL SUMMARY OF CHANGE

**Original Protocol** Version 1.1 – 8 January 2014
**Amendment 1** Version 1.2 – 1 August 2014
**Amendment 2** Version 2.0 – 22 June 2015

**PROTOCOL Version 2.0 – 22 June 2015**

**Summary of change**

Amendment 2 includes significant changes to the eligibility criteria.

New eligibility criteria [*reason for change*]:

Patients must meet ALL of the following criteria in order to be eligible for this study:

1. Aged ≥70 years [*not changed*]
2. Pathologically confirmed solid organ cancer or diffuse large B-cell lymphoma [*permits enrolment of patients with diffuse large B-cell lymphoma who may potentially benefit from the intervention*]
3. Planned for cytotoxic chemotherapy, targeted therapy or immunotherapy [*study no longer restricted to patients with metastatic disease. Any older adult with cancer, regardless of stage of disease, treatment intent, or line of therapy, may potentially benefit from the intervention. Also clarifies definition of chemotherapy, which includes cytotoxic chemotherapy, targeted therapy and immunotherapy*]
4. Able to effectively understand the language of the HRQoL questionnaires in one of the validated languages for the questionnaires [*not changed*]
5. Able to give written informed consent before randomisation according to local, national and international regulations [*not changed*]

Patients who meet any ONE of the following criteria are not eligible for this study:

1. Have received cytotoxic chemotherapy, targeted therapy or immunotherapy within 3 months prior to enrolment [*excludes enrolment of patients who have systemic anti-cancer therapy in the last 3 months that is likely to impact upon the baseline HRQoL responses and increase variability in baseline HRQoL scores, thereby decreasing interpretability of the intervention effects*].
2. Unable to self-complete the HRQoL questionnaires [*not changed*]
3. Any condition (e.g. psychological, geographical, etc.) that does not permit compliance with the protocol [*not changed*]
4. Prior enrolment in this study [*excludes patients from re-enrolment in the study*]

Old eligibility criteria (prior to Amendment 2):

Patients must meet ALL of the following criteria in order to be eligible for this study:

1. Aged ≥70 years
2. Pathologically confirmed solid organ cancer
3. Planned for first-line chemotherapy for metastatic disease, prior to beginning chemotherapy
4. Able to effectively understand the language of the HRQoL questionnaires in one of the validated languages for the questionnaires
5. Able to give written informed consent before randomisation according to local, national and international regulations

Patients who meet any ONE of the following criteria are not eligible for this study:

1. Unable to self-complete the HRQoL questionnaires
2. Any condition (e.g. psychological, geographical, etc.) that does not permit compliance with the protocol

| Change from previous version | Reason | Effect on Study Conduct |
|---|---|---|
| Cover page:<br>➢ Changed text: "~~metastatic~~ cancer receiving ~~first line~~ chemotherapy"<br>➢ Updated version number and date<br>➢ Added dates of amended protocol version and dates | Change in eligibility criteria | Allows recruitment of patients according to new eligibility criteria |
| Page 2:<br>➢ Changed text: "~~metastatic~~ cancer receiving ~~first line~~ chemotherapy"<br>➢ Changed text: "Eastern Health ~~Nelson Road~~ 5 Arnold St Box Hill VIC 3128, Australia | Change in eligibility criteria<br><br>Site address updated | As above<br><br>None |
| Page 7, INTEGERATE Synopsis:<br>➢ Changed text: "~~metastatic~~ cancer receiving ~~first line~~ chemotherapy"<br>➢ Changed text: "~~Metastatic~~ Older adults with solid organ cancer or diffuse large B-cell lymphoma"<br>➢ Deleted text: "Older adults with ~~metastatic~~ cancer receiving chemotherapy"<br>➢ Changed text: "2. Pathologically confirmed solid organ cancer or diffuse large B-cell lymphoma"<br>➢ Changed text: "3. Planned for cytotoxic ~~first line~~ chemotherapy ~~for metastatic disease~~, targeted therapy or immunotherapy ~~prior to beginning chemotherapy~~<br>➢ Added text: "1. Have received cytotoxic chemotherapy, targeted therapy or immunotherapy within 3 months prior to enrolment"<br>➢ Changed text: "2. Unable to self-complete the HRQoL questionnaires"<br>➢ Changed text: "3. Any condition (e.g. psychological, geographical, etc.) that does not permit compliance with the protocol"<br>➢ Added text: "4. Prior enrolment in this study" | Change in eligibility criteria | As above |
| Page 8, INTEGERATE Synopsis:<br>➢ Added text: "stratified according to the following characteristics: treatment intent" | Added variable for minimisation procedure for group allocation to reduce imbalance in variables that may influence primary endpoint | Minimise imbalance between treatment group of an additional variable that may influence primary endpoint |
| Page 9, INTEGERATE Synopsis:<br>➢ Changed text: "~~metastatic~~ cancer receiving ~~first line~~ chemotherapy" | Change in eligibility criteria | As above |
| Page 10, INTEGERATE Schematics of Study Design:<br>➢ Changed text: "~~Metastatic cancer in~~ Adults ≥70 years with cancer~~, prior to~~ commencing cytotoxic ~~first line~~ chemotherapy, targeted therapy, or immunotherapy" | Change in eligibility criteria | As above |
| Page 13, Background:<br>➢ Changed text: "One randomised trial addressed short-term nurse-delivered geriatric intervention by advanced practice nurses" | Update to literature review | None |

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| ➢ Added text: "A recent non-randomised prospective cohort study of 135 older adults with cancer looked at the impact of geriatrician-delivered CGA on chemotherapy toxicity and tolerance.(26) Participants in the intervention cohort underwent risk-stratification using a patient-completed screening questionnaire and high-risk patients received a geriatrician-delivered CGA. Participants in the intervention group were more likely to complete treatment as planned (odds ratio (OR) 4.14 (95% CI: 1.50-11.42), *P*=0.006) and fewer required treatment modification (OR 0.34 (95% CI: 0.16-0.73), *P*=0.006). Whilst there was a trend for fewer in the intervention group to develop grade 3+ toxicity, this did not reach statistical significance." | | |
| Page 14, Background:<br>➢ Changed text: "~~Although~~ Whilst the above studies ~~one pilot study~~ suggest~~s~~ a potential for CGA to improve outcomes ~~interventions~~ in ~~medical oncology~~ older adults with cancer, no randomised controlled trial testing the hypothesis that CGA can improve outcomes in ~~this setting~~the chemotherapy setting has yet been published. In particular, no randomised controlled study has" | Update to literature review | None |
| Page 15, Background:<br>➢ Changed text: "~~metastatic~~ cancer receiving ~~first line~~ chemotherapy" | Change in eligibility criteria | As above |
| Page 17, Background:<br>➢ Added text: "Using the conceptual framework of the International Classification of Functioning, Disability and Health (ICF), the TOI measures activities (i.e. functioning at the level of the individual) and participation (i.e. functioning of a person as a member of society).(42) Therefore, the change in the TOI score of a person represents the overall impact of the physical condition or medical treatment on activities of the person and participation of the person in different areas of life." | Update to literature review | None |
| Page 18, Background:<br>➢ Changed text: "~~metastatic~~ cancer ~~undergoing~~ receiving ~~first line~~ chemotherapy" | Change in eligibility criteria | As above |
| Page 19, Study Objectives:<br>➢ Changed text: "~~metastatic~~ cancer receiving ~~first line~~ chemotherapy" | Change in eligibility criteria | As above |
| Page 20, Study Design and Methods:<br>➢ Changed text: "~~metastatic~~ cancer receiving ~~first line~~ chemotherapy"<br>➢ Changed text: "2. Pathologically confirmed solid organ cancer or diffuse large B-cell lymphoma"<br>➢ Changed text: "3. Planned for cytotoxic ~~first line~~ chemotherapy ~~for metastatic disease~~, targeted therapy or immunotherapy ~~prior to beginning chemotherapy~~<br>➢ Added text: "1. Have received cytotoxic | Change in eligibility criteria | As above |

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|---|---|---|
| chemotherapy, targeted therapy or immunotherapy within 3 months prior to enrolment"<br>➢ Changed text: "2. Unable to self-complete the HRQoL questionnaires"<br>➢ Changed text: "3. Any condition (e.g. psychological, geographical, etc.) that does not permit compliance with the protocol"<br>➢ Added text: "4. Prior enrolment in this study" | | |
| Page 21, Treatment Allocation:<br>➢ Added text: "stratified according to the following characteristics: treatment intent"<br>➢ Added text: "variables required to allocate participants (i.e. treatment intent, tumour type, age, gender" | Added variable for minimisation procedure for group allocation to reduce imbalance in variables that may influence primary endpoint | Minimise imbalance between treatment group of an additional variable that may influence primary endpoint |
| Page 22, Study Intervention:<br>➢ Deleted text: "performance-based assessment of cognition by Montreal Cognitive Assessment (MoCA) ~~and isometric grip strength by a hand dynamometer (refer to **Appendix 12**).~~."<br>➢ Deleted text: "performance-based assessment of functional mobility by TUG ~~and isometric grip strength by a hand dynamometer.~~. | Remove isometric grip strength as part of the protocol as this is no longer considered to be a necessary assessment. | Reduce researcher and participant time required in research-related assessment |
| Page 23, Data Collection:<br>➢ Changed text: "CHSA Clinical Frailty Scale and Timed-Up-and-Go test (TUG)." | Grammatical correction | None |
| Page 28, Study endpoints:<br>➢ Changed text: "~~metastatic~~ cancer receiving ~~first line~~ chemotherapy"<br>➢ Added text: "Overall survival is a secondary endpoint of this study and will be compared between treatment arms in the following pre-specified study groups: (1) palliative-intent treatment subgroup; (2) overall study population; and (3) adjuvant/curative-intent treatment subgroup." | Change in eligibility criteria<br><br>Survival advantage is thought unlikely to be shown in the adjuvant/curative-intent treatment subgroup due to length of follow-up required and power of this study. Therefore, survival analysis will be performed in a pre-specified hierarchical order according to the likelihood of showing a survival advantage. | As above<br><br>Alteration in data analysis |
| Page 29, Study endpoints:<br>➢ Changed text from "The proportion of participants with self-MNA score <11 points and ≥11 points" to "The proportion of participants with self-MNA score ≤11 points and >11 points" | Correction of the cut-off score for the self-MNA. | |
| Page 31, Primary Efficacy Analysis:<br>➢ Changed text: "~~metastatic~~ cancer receiving ~~first line~~ chemotherapy"<br>➢ Added text: "**4.3.3.1. Subgroup Analysis for the Primary Efficacy Endpoint.** In addition to the analysis of the overall study population, pre-specified subgroup analysis will be conducted for the TOI (primary efficacy endpoint) using linear mixed models to detect significant differences in longitudinal change in TOI score between treatment groups in the following subgroups: i) palliative-intent treatment subgroup; and ii) adjuvant/curative-intent treatment subgroup." | Change in eligibility criteria<br><br>Pre-specified confirmatory subgroup analysis. | As above<br><br>Alteration in statistical procedures |

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| Page 32, Secondary Efficacy Analyses:<br>➢ Added text: "Overall survival between treatment groups will be analysed using a closed hierarchical method in the following pre-specified order: (1) palliative-intent treatment subgroup; (2) overall study population; and (3) adjuvant/curative-intent treatment subgroup." | Pre-specified subgroups for survival analysis. | Alteration in statistical procedures |
| Page 41, List of Appendices:<br>➢ Deleted text: "~~12B: Isometric Hand Grip Strength~~"<br>➢ Changed text: "12B ~~12C~~ Montreal Cognitive Assessment (MoCA) version 7.1" | Remove isometric grip strength as part of the protocol as this is no longer considered to be a necessary assessment. | Reduce researcher and participant time required in research-related assessment |
| Page 67, Appendix 12:<br>➢ Deleted text: "~~12B. Isometric Hand Grip Strength. Instructions for Researcher. This test is performed only by participants receiving integrated geriatric care. The purpose of the grip strength test is to measure the maximum isometric strength of the hands and forearm muscles. In a seated position, the participant holds the hand-held dynamometer in the preferred hand with the arms at right angle and the elbow by the side of the body. The handle of the dynamometer is adjusted if required – the base should rest on first metacarpal (heel of palm), while the handle should rest on middle of four fingers. The participant is instructed to squeeze the dynamometer for a practice trial. The practice trial is performed to determine if the procedure is understood by the participant and the grip size is properly adjusted. After the practice, the participant is instructed to squeeze the dynamometer as hard as possible for about 3 to 5 seconds. No other body movement is allowed. The participant should be strongly encouraged to give a maximum effort. The resting period between trials is approximately 30 seconds. Record the results of two trials, the tested hand, the dominant hand and, if applicable, the reason for use of non-dominant hand. The best result of two trials will be used.~~" | As above | As above |
| Page 68, Appendix 12B:<br>➢ Changed text: "12B ~~12C~~ Montreal Cognitive Assessment (MoCA) version 7.1" | As above | As above |

# INTEGERATE
# Is INTEgrated GERiatric Assessment and Treatment Effective in older adults with cancer receiving chemotherapy?
# A Randomised Controlled Study

# Statistical Analysis Plan

**Version: 1**

**Version Date: 28 May 2019**

**INTEGERATE: Is INTEgrated GERiatric Assessment and Treatment Effective in older adults with receiving chemotherapy? A randomised controlled study**


| | |
|---|---|
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# Contents

# 1. Study Objectives

## 1.1. Aim

The aim of this prospective, randomised controlled study was to evaluate the effects of integrated geriatric care on HRQOL and other key clinical outcomes in older adults with cancer receiving chemotherapy (defined as cytotoxic chemotherapy, targeted therapy or immunotherapy).

## 1.2. Objectives

**Primary Objective**

- Assess the effects of integrated geriatric care on HRQOL in older adults with cancer receiving chemotherapy

**Secondary Objectives**

- Assess the effects of integrated geriatric care on survival, function, mood, nutrition, health utilities, chemotherapy delivery, healthcare utilisation and institutionalisation

**Exploratory Objectives**

- Perform a comparative economic evaluation of integrated geriatric care compared to standard care
- Evaluate the interventions that result from integrated geriatric care
- Evaluate the relationship between components of HRQOL and comprehensive geriatric assessment (CGA) with clinical outcomes
- Develop a brief geriatric assessment screening tool and predictive model for older adults with cancer
- Compare the EORTC QLQ-C30 and QLQ-ELD14 with the EQ-5D-5L and EORTC QLU-C10D
- Compare the EQ-5D-5L with the EORTC QLU-C10D

## 1.3. Hypothesis

**Primary Hypothesis**

- That integrated geriatric care decreases the magnitude and rate of decline in HRQOL in adults 70 years or older receiving chemotherapy, compared with standard care.

**Secondary Hypotheses**

- That integrated geriatric care improves overall survival, function, mood, nutrition, health utilities, chemotherapy delivery, healthcare utilisation or institutionalisation in adults 70 years or older receiving chemotherapy, compared with standard care.
- That integrated geriatric care improves overall survival in adults 70 years or older receiving adjuvant/curative-intent chemotherapy, compared with standard care.
- That integrated geriatric care improves overall survival in adults 70 years or older receiving palliative-intent chemotherapy, compared with standard care.

# 2. Study Design and Methods

## 2.1. Study Design

The design was a prospective, open-label, randomised, controlled, parallel group, superiority study of integrated geriatric care versus standard oncology care.

## 2.2. Study Population and Setting

The study included participants aged ≥70 years with cancer receiving chemotherapy. The study was conducted at Eastern Health, a public health organisation in the eastern metropolitan area of Melbourne, Victoria, Australia. Participants were recruited throughout Eastern Health where oncology services are delivered, including Box Hill Hospital (a tertiary acute hospital), Maroondah Hospital (a secondary acute hospital) and Yarra Ranges Health (a community centre providing day oncology and oncology outpatient service).

### 2.2.1. Inclusion Criteria

1. Aged 70 years or older
2. Pathologically confirmed solid organ cancer or diffuse large B-cell lymphoma
3. Planned for cytotoxic chemotherapy, targeted therapy or immunotherapy
4. Able to effectively understand the language of the quality of life questionnaires in one of the validated languages for the questionnaires
5. Able to give written informed consent before randomisation according to local, national and international regulations

### 2.2.2. Exclusion Criteria

1. Have received cytotoxic chemotherapy, targeted therapy or immunotherapy within 3 months prior to enrolment
2. Unable to self-complete the HRQOL questionnaires
3. Any condition (e.g. psychological, geographical, etc.) that does not permit compliance with the protocol
4. Prior enrolment in this study

### 2.2.3. Co-enrolment Guidelines

1. Co-enrolment in other trials is permitted

## 2.3. Treatment Allocation

### 2.3.1. Method of Treatment Allocation

Participants were randomly assigned via a computerised system using the method of minimisation (with a 80:20 random element) to receive integrated geriatric care or standard oncology care in a 1:1 ratio.(1) In this study, minimisation was used to achieve balance between groups using the following characteristics:

- treatment intent
- tumour type
- age
- gender
- ECOG performance status (physician-rated)

An 80:20 random element was determined to be the optimal value to reduce predictability whilst retaining balance.(2) This method was conducted using the MinimPy software package by a researcher not involved in the care of the study participants.(3)

# 2.4. Study Intervention

## 2.4.1. Integrated Geriatric Care

Participants assigned to the intervention arm of the study will receive integrated geriatric care, in addition to standard oncology care (refer to **2.4.2**). Integrated geriatric care consists of a comprehensive geriatric assessment and management performed by the study doctor who is a consultant physician in the specialty of Geriatric Medicine. It has two essential components: the process of assessment coupled with an appropriate management plan.

The assessment should as a minimum cover:

- current active medical problems
- past medical history
- medication review
- immunisation status
- advanced care planning arrangements
- current and previous physical functioning
- psychological functioning including cognition and mood
- social function including living arrangements, financial arrangements, community services, social support and carer issues

The PRO measures collected at baseline assessment (except for the HRQOL questionnaires) and timed-up-and-go test (TUG) will form a component of the comprehensive geriatric assessment and will be available to the study doctor. Additional components of the comprehensive geriatric assessment will be collected using an additional self-reported questionnaire (refer to **Appendix 11**). This self-reported questionnaire is based on a modification of the Adelaide Tool(4) and the Cancer and Aging Research Group's predictive model for chemotherapy toxicity(5), and includes:

- Medical Outcome Survey (MOS) Core Survey items on general health, health change, ability to walk 1 block and social activity limitation because of physical/emotional health
- MOS Social Support Survey items on tangible support (4 of 4 items) and emotional social support (1 of 8 items),
- Older Americans Resources and Services (OARS) items on hearing and vision
- number of falls in the last 6 months
- Center for Epidemiologic Studies Depression scale (CES-D) items on exhaustion
- pain numerical rating scale
- Distress Thermometer and Canadian Problem Checklist (20 of 21 items; one item on practical problems related to work/school was not included because it was thought not relevant to the study population's age-group)

The remainder of the assessment and development of the management plan must include a personal attendance by the study doctor. This attendance should include performance-based assessment of cognition by Montreal Cognitive Assessment (MoCA). A prioritised list of diagnoses/problems will be developed based on the information derived from the history and examination, and any additional information provided by other means, including an interview of a person other than the patient.

The management plan will be individualised to the patient's needs and may include:

- measures to optimise concurrent health issues
- medication recommendations
- non-medication recommendations (e.g. lifestyle changes, including exercise and diet)
- assessment of the risk of chemotherapy toxicity
- referrals to relevant existing hospital and community services (e.g. allied health services, rehabilitation services, aged care services, palliative care services)

The management plan should be explained and, if necessary, provided in written form to the patient or, where appropriate, their family or carer(s). A written report of the comprehensive geriatric assessment and management plan will be communicated back to the treating oncologist and general practitioner within a maximum of 2 weeks of the assessment via email or mail. More prompt verbal communication may be appropriate.

Participants assigned to the intervention arm will receive a comprehensive geriatric assessment and management within 3 weeks of randomisation. Participants assigned to the intervention arm will continue to see their oncologists who are the participants' primary physician for treatment of their cancer and related health conditions. Further reviews with the study doctor will occur at approximately 12 weeks and 24 weeks after randomisation. The 12 weeks and 24 weeks reviews should include performance-based assessment of functional mobility by TUG. Additional reviews with the study doctor may be scheduled as required depending on medical needs.

Assessments of outcome measures occur at 12 weeks, 18 weeks and 24 weeks following randomisation. After 24 weeks, participants in the intervention arm may continue to receive integrated geriatric care but will not be required to complete further study assessments.

## 2.4.2. Standard Oncology Care

Participants assigned to the control arm will receive standard oncology care provided by their oncologist and will not have any further contact with the study doctor following randomisation. The treating clinicians will be blinded to the results of any study assessments. Assessments of outcome measures occur at 12 weeks, 18 weeks and 24 weeks following randomisation. After 24 weeks, participants will no longer be required to complete further study assessments. Although participants in the control arm may be referred to a geriatrician at any time by their treating clinicians, they will not be permitted to cross-over to receive the study-specific comprehensive geriatric assessment and management.

## 2.5. Data

### 2.5.1. Collected Data

| Required Forms | Baseline | Week 12 | Week 18 | Week 24 / End of Study |
|---|---|---|---|---|
| **PARTICIPANT FORMS** | | | | |
| Participant Information and Consent Form | X | | | |
| Medicare Participant Consent Form (optional) | X | | | |
| Global Rating of Change | | X | X | X |
| ELderly Functional Index (ELFI) | X | X | X | X |
| EORTC QLQ-C30 v3.0 and QLQ-ELD14 | X | X | | X |
| EQ-5D-5L | X | X | X | X |
| Function – ECOG, KPS, ADL, IADL | X | X | | X |
| Mood – PHQ-9 and GAD-7 | X | X | | X |
| Nutrition – self-MNA and G8 Screening Tool | X | X | | X |
| Social situation | X | X | | X |
| **RESEARCHER FORMS** | | | | |
| Demographics | X | | | |
| Medical History (including Charlson Comorbidity Index) | X | | | |
| Concurrent medications | X | X | | X |
| TUG | X | intervention group | | intervention group |
| Physician-rated ECOG and KPS | X | intervention group | | intervention group |
| CHSA Clinical Frailty Scale | X | intervention group | | intervention group |
| Flemish Triage Risk Screening Tool (fTRST) | X | intervention group | | intervention group |
| Level of care | X | X | | X |
| Height | X | | | |
| Weight | X | X | | X |
| Blood test results (FBE, UEC) | X | | | |
| Chemotherapy treatment | | X | | X |
| Healthcare utilisation | | X | | X |
| CoMiDa Form | X | X | X | X |
| Overall survival | To cut-off date (to be determined) | | | |

# 2.6. Endpoints

## 2.6.1. Summary of Endpoints

The primary and secondary endpoints are summarised in the table below. The primary endpoint of this study is health-related quality of life (HRQOL). The secondary endpoints are survival, function, mood, nutrition, chemotherapy delivery, healthcare utilisation and institutionalisation.

| Primary Endpoint | Measures |
|---|---|
| **ELderly Functional Index (ELFI)** | The ELderly Functional Index (ELFI) consists of the linear transformation from 0-100 of the unweighted summed score of 12 items from the QLQ-C30 and QLQ-ELD14, covering: physical functioning (PF2; QLQ-C30 items 1-5), role functioning (RF2; QLQ-C30 items 6-7), social functioning (SF; QLQ-C30 items 26 and 27) and mobility (MO; QLQ-ELD14 items 31, 33 and 34).<br><br>The individual scales on the QLQ-C30, QLQ-ELD14 and EQ-5D-5L will be reported in the secondary and tertiary HRQOL analyses to assist in interpretation of the primary endpoint. |
| **Secondary Endpoints** | **Measures** |
| **Survival** | • Overall survival |
| **Function** | • Self-reported ECOG performance status<br>• Self-reported Karnofsky performance status<br>• Katz ADL scale<br>• OARS IADL scale |
| **Mood** | • PHQ -9<br>• GAD-7 |
| **Nutrition** | • Self-MNA |
| **Health Utilities** | • EQ-5D-5L |
| **Chemotherapy delivery** | • Initial dose (standard or reduced dose)<br>• Subsequent dose (dose delay or dose reduction, discontinuation of chemotherapy) |
| **Healthcare utilisation** | • Hospitalisation (number, type, length of hospital stay, reason)<br>• Emergency department visits (number, reason)<br>• Referrals (type, date referred, date seen) including Allied Health and Oncology Rehabilitation Program<br>• Medical consultations<br>• Type of Pharmaceutical Benefit Scheme (PBS)-listed medications |
| **Institutionalisation** | • Social situation<br>• Level of care |

# 2.7. Study endpoints

## 2.7.1. Primary Endpoint

The primary objective of this study was to assess the effects of integrated geriatric care on HRQOL in older adults (>70 years) with cancer receiving chemotherapy. The EORTC QLQ-C30 version 3.0, QLQ-ELD14 and EQ-5D-5L will be used to measure HRQOL.

The primary endpoint of this study was the ELderly Functional Index (ELFI). Previous versions of the study protocol designated the ELFI as the Trial Outcome Index, but the endpoint definition remains unchanged (i.e. ELFI = Trial Outcome Index).

ELFI consists of the linear transformation from 0 to 100 of the unweighted summed score of 12 items from the QLQ-C30 and QLQ-ELD14, covering: physical functioning (PF2; QLQ-C30 items 1-5), role functioning (RF2; QLQ-C30 items 6-7), social functioning (SF; QLQ-C30 items 26 and 27) and mobility (MO; QLQ-ELD14 items 31, 33 and 34). A higher score on the ELFI represents higher ("better") functioning. The individual scales on the QLQ-C30, QLQ-ELD14 and EQ-5D-5L will be reported in the tertiary HRQOL analyses to assist in interpretation of the primary endpoint and to provide a comprehensive assessment of the impact of the intervention on all domains of HRQOL assessed. Note that most of these scales contain multiple items (multi-item scales), whilst the remainder contain only one item (but are still called scales). Following convention, we will not report or analyse separately any items that are aggregated into multi-item scales.

## 2.7.2. Secondary Endpoints

### 2.7.2.1. Overall Survival

Overall survival is defined as the time from randomisation until death due to any cause. Participants who are alive (including lost to follow-up) at the time of the analysis will be censored at the date when they were last known to be alive.

### 2.7.2.2. Performance status

Performance status is used to assess functional performance in cancer patients and is part of routine oncology care. Performance status is a powerful predictor of HRQOL and survival and is an important concern in cancer patients. ECOG and KPS are both widely used methods of assessing performance status of cancer patients. Self-rated ECOG and KPS score will be used to describe the performance status of the study population.

The ECOG score is a single item rating of the degree to which the patient is able to participate in typical activities without a need for rest. The scale ranges from 0 (fully active) to 5 (dead) (6) The KPS score is a single item rating of three dimensions of functional status: activity, work and self-care.(7) The KPS is an 11-point rating scale that ranges from 0 (dead) to 100 (normal functioning).

### 2.7.2.3. Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL)

In geriatric medicine, ADL and IADL is used to assess functional status and is part of routine geriatric assessment.(8) Decline in functional status is associated with adverse health outcomes such as mortality and residential care placement for older hospitalised patients. Self-reported Katz ADL scale and OARS IADL scale will be used to describe the functioning level in of the study population.(9, 10)

Katz ADL scale assesses adequacy of performance in basic activities of daily living: bathing, dressing, toileting, transferring, continence, and feeding. Each item are scored yes/no for independence in each of the six functions. A summary score ranges from 0 (unable to perform any activity) to 6 (able to perform all activities).

OARS IADL is an easy to administer assessment instrument that provides self-reported information about functional skills necessary for independent living in the community. These skills are considered more complex than the basic activities of daily living as measured by the Katz ADL scale. The 7-items on the OARS IADL assesses the following domains of function: telephone, shopping, food preparation, housekeeping, mode of transportation, medications and finances. Each item is scored on a 3-point Likert-like scale, with the total score ranging from 0 (unable to perform any activity) to 14 (able to perform all activities).

Disability in ADL and IADL is defined as the need for assistance to complete at least one ADL or IADL, respectively. Functional decline in ADL and IADL is defined as any decrease in ADL and/or IADL score between baseline and follow-up assessments.

#### 2.7.2.4. Mood

Anxiety and depression are common symptoms in patients with advanced cancer. Integrated geriatric care may alleviate some of these symptoms by provided additional support and reducing social isolation.

PHQ-9 and GAD-7 will be used to measure the prevalence of depression and anxiety in the study population. PHQ-9 and GAD-7 are subscales of the Patient Health Questionnaire, a patient self-rated version of the Primary Care Evaluation of Mental Disorders which is a widely used screening tool for mental health disorders in primary care.(11)

The PHQ-9 is a brief, self-rated questionnaire that was developed to screen for depression. It has 9-items derived from the Diagnostic and Statistical Manual of Mental Disorders, 4$^{th}$ Edition, Text Revision (DSM-IV-TR) criteria for major depressive disorder.(12) For each item the participant is asked to rate how much over the 2 weeks they have been bothered by the symptoms. Scoring is on a Likert-type scale from 0 to 3 (0 indicates not at all; 1 indicates several days; 2 indicates more than half the days; 3 indicates nearly every day). The PHQ-9 scored as a continuous measure has good discriminating power between cases and non-cases of major depressive disorder in cancer outpatients, with an area under the curve (AUC) of 0.94 (95% confidence interval [CI], 0.93-0.95) on ROC analysis.(13)

The GAD-7 is a brief, self-rated questionnaire which was originally developed as a screen for Generalised Anxiety Disorder (GAD), and is frequently used in conjunction with the PHQ-9.(14) Scoring of its 7-item is on a Likert-type scale from 0 to 3 (0 indicates not at all; 1 indicates several days; 2 indicates more than half the days; 3 indicates nearly every day). Anxiety in cancer is thought to be most closely related to the free floating anxiety characteristic of GAD.(15). The GAD-7 is gaining use in screening for a range of anxiety disorders due to its brevity and good psychometric properties.

An estimate of clinical important levels of depression and anxiety can be made using cut-off scores for PHQ-9 and GAD-7. Scores of 5, 10, 15 represent cutpoints for mild, moderate, and severe levels of depression and anxiety, on the PHQ-9 and GAD-7 respectively.(14) A recommended cutpoint for further evaluation and treatment is a score of 10 or more on both measures.(14) A score of 9 or less requires no action or monitoring.

#### 2.7.2.5. Nutrition

The self-MNA will be used to describe the nutritional status in the study population. The MNA is a nutritional screening instrument which was especially developed and validated for use in the elderly.(16) The fully validated self-completed version of the MNA (self-MNA) consists of 6-items which are scored between 0 and 14. (17) The self-MNA takes 3 minutes to complete and is as effective as the full MNA to identify malnutrition.(17) A full MNA score of $\leq$23.5 has been shown in to be a predictor of early death in older adults treated with first-line chemotherapy for cancer.(18) A self-MNA score of $\leq$11 points is considered to be equivalent to a full MNA score of $\leq$23.5. Standard score interpretation for the self-MNA are: 0-7 = malnourished, 8-11 = at risk of malnutrition, 12-14 = normal nutritional status.

#### 2.7.2.6. Health Utilities

The EQ-5D-5L will be used to describe the health utilities in the study population and as part of the health economic analysis.

#### 2.7.2.7. Chemotherapy Delivery

Chemotherapy delivery will be assessed over the 24 weeks period from start of chemotherapy by dose intensity, dose reduction and treatment delays. Relative dose intensity (RDI) will be calculated based on the ratio of delivered dose intensity of chemotherapy to standard dose for the time period.

#### 2.7.2.8. Healthcare Utilisation

Healthcare utilisation is an important consideration in healthcare service delivery. By improving support to participants, integrated geriatric care may potentially reduce the rate of emergency department visit, unplanned hospital admissions and length of hospital stay. Data on cause and duration of any emergency department visits or hospital admissions during the study period will be extracted from participant's hospital record.

#### 2.7.2.9. Institutionalisation

Social situation and level of care will be used to determine institutionalisation in the study population. Social situation differentiates between living at home alone, home with others or residential care. Level of care is determined by the Aged Care Assessment Service (ACAS) and differentiates between independent, low level care and high level care. For participants who are admitted to hospital, rehabilitation facility or palliative care facility at the time of assessment, the social situation and level of care is considered to be the discharge destination and level of care on discharge, respectively. Institutionalisation is defined in this study as residing in a residential aged care facility.

# 3. Statistical Procedures

## 3.1. Overview

All analyses will be conducted as defined in a formal statistical analysis plan (SAP) for the analysis and presentation of data. The SAP will be finalised prior to commencement of study analysis and approved by the Trial Management Committee (TMC).

This document constitutes the formal statistical analysis plan (SAP).

All analyses will be conducted according to the intention-to-treat (ITT) principle: all eligible and evaluable participants will be included in the analysis and analysed according to the arm randomised to (using the as-randomised participant population). By using the ITT principle, the benefits of randomisation are maintained (i.e. that the trial arms are similar except for intervention).

Baseline characteristics by treatment arm will be summarised in frequency tables and by use of descriptive statistics for quantitative variables. Univariate associations will be identified using independent T-test for comparing means, $\chi 2$ or Fisher's exact test for comparing categorical data. Confounder bias will be minimised with logistic regression by adjusting for age plus other relevant differences between the groups (comorbidity, metastatic disease, chemotherapy dose reduction at the outset) in bivariate and multivariate analysis.

Summary tables will be prepared giving numbers of participants by treatment arm and by randomisation irregularities, treatment compliance, eligibility infringements, and losses to follow-up (as per CONSORT guidelines).(19)

*Table 1. Baseline characteristics by treatment group*

| Characteristic | Intervention | Usual Care |
|---|---|---|
| Age | | |
| Mean | | |
| Median | | |
| Range | | |
| Sex | | |
| Male | | |
| Female | | |
| Marital status | | |
| Married | | |
| Separated, divorced | | |
| Widowed | | |
| Single | | |
| Household composition | | |
| Lives in the community with spouse, partner or child | | |
| Lives in the community alone | | |
| Lives in residential care | | |
| Cancer site | | |
| Upper gastrointestinal | | |
| Lower gastrointestinal | | |
| Lung | | |
| Urogenital | | |
| Breast | | |
| DLBCL | | |
| Other, not specified | | |
| Cancer stage | | |
| II | | |
| III | | |
| IV | | |

| | | |
|---|---|---|
| Treatment intent | | |
| Curative/neoadjuvant/adjuvant | | |
| Palliative | | |
| Initial anti-cancer treatment | | |
| Cytotoxic chemotherapy | | |
| Immunotherapy | | |
| Targeted therapy | | |
| Treatment line | | |
| 1st line | | |
| 2nd line | | |
| 3rd line and beyond | | |
| Patient-reported outcomes | | |
| ELFI score | | |
| EQ-5D-5L utility score | | |
| ECOG 0-1 | | |
| KPS ≥80 | | |
| IADL unimpaired | | |
| ECOG 0-1 | | |
| KPS ≥80 | | |
| PHQ-9 | | |
| GAD-7 | | |

# 3.2. Sample size

## 3.2.1. Sample size required

Based on reviews of published studies, a minimal important difference in patient-reported outcome scores has commonly been set at approximately half the standard deviation; that is, equivalent to an effect size of 0.50.(20, 21) An effect size of 0.5 is commonly regarded as a medium difference and a meta-analysis has shown it to be clinically relevant in studies of quality of life using QLQ-C30 as an outcome measure.(22, 23)

The target sample for this study was based on an independent t-test at a 2-sided significance level of 0.05 to have an 80% power to detect a significant between-group difference in ELFI from baseline to 12 weeks with an effect size of 0.5. Under these assumptions, the minimum sample size is 64 evaluable participants in each group (or a total of approximately 128 evaluable participants) who have completed the primary outcome measure at two separate timepoints.

# 3.3. Baseline Characteristics

# 3.4. Primary Efficacy Analysis: HRQOL

## 3.4.1. Overview

The primary efficacy analysis will address the primary objective of this study which is to assess the effects of integrated geriatric care on HRQOL in older adults with cancer receiving chemotherapy. This will involve a hierarchical set of HRQOL analyses, described below as the primary, secondary and tertiary HRQOL analyses.

The primary HRQOL analysis will relate to the primary endpoint of the study, the ELFI, which represents the subset of HRQOL domains most likely affected by the study intervention. The primary HRQOL analysis will employ linear mixed models, with pattern-mixture models and/or joint model of longitudinal and survival data as sensitivity analyses. The secondary HRQOL analyses will also relate to the ELFI and compare: i) the proportions of participants who experience change in ELFI by at least the clinically important threshold, using Fisher's test; and ii) time to change in ELFI by at least the clinically important threshold using log-rank test. Finally, the tertiary HRQOL analyses involve analyses of all the scales of the EORTC QLQ-C30, QLQ-ELD14 and EQ-5D-5L using t-test or Wilcoxon test (according to normality of distribution), to complement the primary and secondary HRQOL analyses, to make full use of all HRQOL data collected and to assist in interpretation of the of the primary endpoint.

## 3.4.2. Missing PRO data

Missing data can be classified by:

i. Extent of missingness:
   - missing items (one or more missing responses within a questionnaire); or
   - missing forms (the whole questionnaire is missing for a patient)

ii. Reason for missingness:
   - missing completely at random (MCAR): missing data is independent of all responses (i.e. loss completely by chance); or
   - missing at random (MAR): missing data depends on other observed responses but independent of the value of the unobserved response; or
   - missing not at random (MNAR): missing data depends on the value of the unobserved response

There are two important potential consequences of missing PRO data: (1) decreased precision (wider confidence intervals) and less power to detect statistically significant differences; (2) potential for bias in the estimation of both between (e.g. treatment effect) and within group effects (e.g. change over time).(24) For example, in oncology, patients who are sicker may be less likely to complete HRQOL questionnaires which may potentially overestimate HRQOL and underestimate the adverse effects of cancer and cancer therapy.

### 3.4.2.1. Missing HRQOL data patterns

Prior to conducting analyses of HRQOL data, rates and reasons for missing PRO questionnaires will be summarised to assess the extent to which data are missing at random. This is an important first step, as it aids interpretation of the results of HRQOL outcome analyses relative to the assumptions of those analyses.

A table of HRQOL completion rates by arm will be reported. Following NCIC Clinical Trials Group (NCIC CTG) recommendations(25), completion rates at each follow-up timepoint will be calculated in two ways, that is, HRQOL assessments completed as a percentage of: 1) all participants recruited (i.e. number of baseline HRQOL completions); 2) number of HRQOL assessment expected (i.e. number of participants still alive and on-study at that timepoint).

***Table 2. Rate and reasons for missing ELFI data***

| | **All Study Participants (N=)** | | | |
|---|---|---|---|---|
| **Status/Reason** | **Week 0** | **Week 12** | **Week 18** | **Week 24** |
| | N (%) | N (%) | N (%) | N (%) |
| Completed | | | | |
| Patient refused | | | | |
| Patient feels too ill | | | | |
| Staff felt patient too ill | | | | |
| Staff oversight | | | | |
| Other, not specified | | | | |

| | | | | |
|---|---|---|---|---|
| Unknown | | | | |
| Patient death | | | | |
| % of surviving patients | | | | |
| % of total patients | | | | |

***Table 3. Rate and reasons for missing ELFI data, according to treatment groups***

| | Intervention Group (N=) | | | | Usual Care Group (N=X) | | | |
|---|---|---|---|---|---|---|---|---|
| **Status/Reason** | **Week 0** | **Week 12** | **Week 18** | **Week 24** | **Week 0** | **Week 12** | **Week 18** | **Week 24** |
| | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) |
| Completed | | | | | | | | |
| Patient refused | | | | | | | | |
| Patient feels too ill | | | | | | | | |
| Staff felt patient too ill | | | | | | | | |
| Staff oversight | | | | | | | | |
| Other, not specified | | | | | | | | |
| Unknown | | | | | | | | |
| Patient died | | | | | | | | |
| % of surviving patients | | | | | | | | |
| % of total patients | | | | | | | | |

To explore mechanisms of missingness, a graph of the ELFI versus time will be graphed, stratified by dropout time.(24) If the trajectories over time are substantially different, this will suggest data are not missing completely at random. For example, if participants who have lower baseline values are more likely to drop out, or if steeper rates of decrease in ELFI over time are associated with earlier dropout, missing data are more likely to be linked with sicker participants. We will also use these graphs to assess whether the separation between the missingness patterns is more dramatic in the intervention arm than the control arm.

### 3.4.2.2. Handling of missing PRO data: primary efficacy analysis

When at least half of the items from the relevant EORTC QLQ scale have been answered, scores for missing items will be assigned the mean score of the completed items from the relevant scale. If more than half the items are missing, then the scale score is missing.

#### 3.4.2.3. Handling of missing PRO data: secondary efficacy analyses

The following imputation method will be applied prior to performing the relevant statistical test:

| PRO | Imputation for Missing Item(s) | Imputation for Missing Form(s) |
|---|---|---|
| ECOG-PS | If KPS has been answered, scores for missing ECOG-PS will be imputed by multiple imputation using predictive mean matching | None |
| KPS | If ECOG-PS has been answered, scores for missing KPS-PS will be imputed by multiple imputation using predictive mean matching | None |
| ADL | If at least half of the items from the scale have been answered, scores for missing items will be assigned the mean score of the completed items | None |
| IADL | If at least half of the items from the scale have been answered, scores for missing items will be assigned the mean score of the completed items | None |
| PHQ9 | If one or two values are missing from the score, then they can be substituted by the average score of the non-missing items. (instrument instructions) | None |
| GAD7 | If one or two values are missing from the score, then they can be substituted by the average score of the non-missing items. (instrument instructions) | None |
| Self-MNA | If at least half of the items from the scale have been answered, scores for missing items will be imputed by multiple imputation using predictive mean matching | None |
| G8 score | If at least half of the items from the scale have been answered, scores for missing items will be imputed by multiple imputation using predictive mean matching | None |
| EQ-5D-5L | If at least 60% of the domains have been answered, scores for missing domains will be imputed by multiple imputation using predictive mean matching | None |

## 3.4.3. Primary HRQOL Analysis

The primary HRQOL analysis is defined prospectively as a comparison of the longitudinal change in ELFI scores for significant between-group difference using linear mixed models. The models will include baseline variables (baseline ELFI score, and possibly other baseline variables predictive of ELFI outcome) as covariates and treatment arm and time (and their interaction) as fixed effects. Time will include the baseline, 12 week, 18 week and 24 week assessment points. Time is continuous in linear mixed model.

These models account for covariance between repeated measures on participants and will be used to: i) describe the time course of the ELFI over time; ii) assess whether the time course differs between the two treatment arms by testing the study arm-by-time interaction; and iii) estimate and test differences between the two treatment arms at specific time points of interest via selected linear contrasts.

Linear mixed models account for missing data by using information from the observed data to implicitly impute unobserved data.

#### 3.4.3.1. Subgroup Analysis for the Primary Efficacy Endpoint

In addition to the analysis of the overall study population, subgroup analysis will be conducted for the ELFI (primary efficacy endpoint) using linear mixed models to detect significant differences in longitudinal change in ELFI score between treatment groups in the following subgroups: i) palliative-intent treatment subgroup; and ii) adjuvant/curative-intent treatment subgroup.

#### 3.4.3.2. Sensitivity Analyses

Sensitivity analyses will be performed using pattern-mixture models and/or joint model of longitudinal and survival data to help interpret results if greater than 20% of the ELFI data are missing, and if reasons for missing data (from the CoMiDa form) and patterns of missing data suggest that these when data are not missing at random.

### 3.4.4. Secondary HRQOL Analyses

Secondary HRQOL analyses, defined prospectively, includes: i) comparison of the proportions of participants in the two treatment arms with at least 10 units deterioration in ELFI score at 12 weeks, 18 weeks and 24 weeks by using Fisher's exact test (as recommended by NCIC CTG)(25); and ii) time to deterioration in ELFI score (defined as the time from randomisation to a minimum 10 units deterioration in change score from baseline) by log-rank test.

### 3.4.5. Tertiary HRQOL Analyses

Tertiary HRQOL analyses will be performed on all scales of the EORTC QLQ-C30, QLQ-ELD14 and EQ-5D-5L to complement primary and secondary HRQOL analyses, to make full use of all HRQOL data collected, and to assist in interpretation of the primary endpoint. The t-test or Wilcoxon test will be applied, depending on normality of distribution, to each of the scales of the QLQ-C30 and QLQ-ELD14 (using the EORTC's standard scoring algorithms) and the EQ-5D-5L, to assess between-group differences in change from baseline to 12 weeks, 18 weeks and 24 weeks, across a comprehensive range of HRQOL domains. The ELFI will also be analysed in this way for completeness.

### 3.4.6. Adjustment for Multiple Hypothesis Testing

For the primary HRQOL analysis, adjustment for multiple comparisons of ELFI differences at specific times will be undertaken using the Hochberg method.(26) No formal adjustment will be used for other secondary or exploratory analyses. In general, two-sided P-values will be used and 95% confidence limits for all important endpoints will be reported.

## 3.5. Secondary Efficacy Analyses

### 3.5.1. Overall Survival

Overall survival between treatment groups will be analysed using a closed hierarchical method in the following pre-specified order: (1) palliative-intent treatment subgroup, (2) overall study population; and (3) adjuvant/curative-intent treatment subgroup.

Overall survival will be estimated using the non-parametric Kaplan-Meier method. Summary statistics will be presented with appropriate confidence intervals. The non-parametric log rank test will be used to compare the two arms of the study and, if appropriate, a Cox proportional hazard model will be used to estimate the treatment effects.

### 3.5.2. Other Secondary Endpoints

Other secondary endpoints will be summarised according to established guidelines specific to the measurement instrument. In general, categorical variables will be tabulated and key summary statistics (mean, standard deviation, median, range, etc.) will be presented for continuous measurements. Comparisons between treatment arms will be made where appropriate and the test selected depending on the distribution.

Secondary endpoints were specified in the protocol as follows:

- Performance Status The mean self-rated ECOG score and KPS score of patients at 12 weeks and 24 weeks are secondary endpoints; they will be compare d between treatment arms.
- Functional Status The proportion of participants in each treatment arm with functional decline in the ADL and/or IADL scores at 12 weeks and 24 weeks are secondary endpoints of this study; they will be compared between treatment arms.
- Mood The proportion of participants in each of the PHQ-9 and GAD-7 categories (cut-points 5, 10 and 15) in the two treatment arms at 12 weeks and 24 weeks are secondary endpoints of this study; they will be compared between treatment arms.
- Nutrition The proportion of participants with self-MNA score ≤11 points and >11 points in the two treatment arms at 12 weeks and 24 weeks is a secondary endpoint of this study and will be compared between treatment arms.
- Health Utility The EQ-5D-5L health utility score in the two treatment arms at 12 weeks and 24 weeks are secondary endpoints of this study and will be compared between treatment arms.
- Chemotherapy delivery Secondary endpoints of this study are the mean RDI of chemotherapy, the proportion of participants with dose reduction ≥10% from previous dose; they will be compared between treatment arms.
- Healthcare utliisation Secondary endpoints of this study are the mean number of: emergency department visits, hospital admissions (including length of hospital stay; and divided into planned and unplanned), medical consultations and type of PBS-listed medications in the two treatment arms from randomisation to 12 weeks and 24 weeks post-randomisation; they will be compared between treatment arms. An additional secondary endpoint is the hazard ratio for hospitalisation of participants in the two treatment arms; this will be compared between treatment arms.
- Institutionalisation A secondary endpoint of this study is the hazard ratio of institutionalisation of participants in the two treatment arms; this will be compared between treatment arms. In addition, the level of care level of care and social situation will also be described in the treatment arms.

The following endpoint definition was changed from the protocol:

- Chemotherapy delivery: the proportion of participants with dose delays in the two treatment arms at 12 weeks and 24 weeks. Dose delay is defined as a delay of more than 3 days in the start of chemotherapy measured since the start of the previous cycle.

The following endpoints were not defined in the protocol, but will be analysed as exploratory endpoints to supplement the pre-specified secondary endpoints:

- QLU-C10D health utility
- QLU-C10D health utility score in the two treatment arms at 12 weeks and 24 weeks will be compared between treatment arms.(27, 28)
- The QLU-C10D health utility scores will also be used in the health economic analysis, in place of the EQ-5D-5L scores, to determine if the same or different conclusions would be reached with either utility measure.
- Chemotherapy delivery
- Primary dose reduction (PDR) will be compared within treatment arms. PDR is defined as dose of chemotherapy which is less than the dose recommended for given regimen in current treatment guidelines by NCCN (excluding round-off).
- Mean % dose reduction at outset will be compared within treatment arms.
- Median % dose reduction at outset will be compared within treatment arms.
- Early discontinuation of chemotherapy will be compared within treatment arms.
- Mean cycles of chemotherapy delivered will be compared within treatment arms.
- Median cycles of chemotherapy delivered will be compared within treatment arms.

*Table 4. Summary of secondary and additional exploratory endpoints, data type, data timepoints and statistical tests are listed in the table below.*

| Endpoints | Data Type | Data output | Data Timepoints | Statistical Tests |
|---|---|---|---|---|
| **Function** | | | | |
| ECOG-PS | Categorical ordinal<br>(0,1,2,3,4) | contingency table | Baseline<br>Wk12<br>Wk24 | contingency table analysis |
| KPS | Categorical ordinal<br>(30,40,50,60,70,80,90,100) | contingency table | Baseline<br>Wk12<br>Wk24 | contingency table analysis |
| Katz ADL scale | 6-item, categorical dichotomous scale<br>(i) → dichotomous outcome (unimpaired, impaired)<br>(ii) → dichotomous outcome (any decrease in ADL) | 1. unimpaired vs impaired<br>2. decrease in ADL | Baseline<br>Wk12<br>Wk24 | contingency table analysis |
| OARS IADL | 7-item, 3-point Likert scale<br>(i) → categorical dichotomous (unimpaired, impaired)<br>(ii) → categorical dichotomous (any decrease in IADL) | 1. unimpaired vs impaired<br>2. decrease in IADL | Baseline<br>Wk12<br>Wk24 | contingency table analysis |
| **Mood** | | | | |
| PHQ9 (depression) | 9-item, 4-point Likert scale<br>→ categorical ordinal (none, mild, moderate, severe)<br>→ categorical dichotomous (not depressed, depressed) | contingency table | Baseline<br>Wk12<br>Wk24 | contingency table analysis |
| GAD7 (anxiety) | 9-item, 4-point Likert scale<br>→ categorical ordinal (none, mild, moderate, severe)<br>→ categorical dichotomous (not anxious, anxious) | contingency table | Baseline<br>Wk12<br>Wk24 | contingency table analysis |
| **Nutrition** | | | | |
| Self-MNA | 6-item questionnaire<br>→ categorical dichotomous (malnourished/at risk vs normal)<br>→ categorical ordinal (malnourished, at-risk, normal) | 1. malnourished/at risk vs normal<br>2. malnourished vs at-risk vs normal<br>3. decrease in self-MNA | Baseline<br>Wk12<br>Wk24 | contingency table analysis |
| **Health Utilities** | | | | |
| EQ-5D-5L | 5-item, 5-point Likert scale, weighted with Australian utility weights | mean utility weight | Baseline<br>Wk12<br>Wk18<br>Wk24 | t-test (parametric); or Mann-Whitney test (non-parametric) |
| QLU-C10D | 10-dimensions derived from 13 items of the QLQ-C30, each dimension weighted with Australian utility weights | mean utility weight | Baseline<br>Wk12<br>Wk18<br>Wk24 | t-test (parametric); or Mann-Whitney test (non-parametric) |
| **Chemotherapy Delivery** | | | | |
| Initial dose (i.e. primary dose reduction) | Categorical dichotomous<br>(full dose, reduced dose) | full dose vs reduced dose | Baseline | contingency table analysis |
| Mean % dose reduction at outset where applicable | Numerical | mean | Baseline | t-test (parametric); or Mann-Whitney test (non-parametric) |
| Median % dose reduction at outset where applicable | Numerical | median | Baseline | Mann-Whitney test (non-parametric) |
| Subsequent dose reduction ≥10% | Categorical dichotomous<br>(yes, no) | yes vs no | | contingency table analysis |
| Subsequent dose escalation | Categorical dichotomous<br>(yes, no) | yes vs no | | contingency table analysis |
| Dose delay >3 days | Categorical dichotomous<br>(yes, no) | yes vs no | | contingency table analysis |

| | | | | |
|---|---|---|---|---|
| Early discontinuation | Categorical dichotomous (yes, no) | yes vs no | | contingency table analysis |
| Mean Relative Dose Intensity (RDI) | Numerical | mean | | t-test (parametric); or Mann-Whitney test (non-parametric) |
| Mean cycles delivered | Numerical | mean | | t-test (parametric); or Mann-Whitney test (non-parametric) |
| Median cycles delivered | Numerical | Median | | Mann-Whitney test (non-parametric) |
| **Healthcare Utilisation** | | | | |
| Mean number of emergency department visits | Numerical | mean | Baseline<br>Wk12<br>Wk18<br>Wk24 | t-test (parametric); or Mann-Whitney test (non-parametric) |
| Mean number of hospital admissions (total) | Numerical | mean | Baseline<br>Wk12<br>Wk18<br>Wk24 | t-test (parametric); or Mann-Whitney test (non-parametric) |
| Mean number of hospital admissions (unplanned) | Numerical | mean | Baseline<br>Wk12<br>Wk18<br>Wk24 | t-test (parametric); or Mann-Whitney test (non-parametric) |
| Mean number of hospital admissions (planned) | Numerical | mean | Baseline<br>Wk12<br>Wk18<br>Wk24 | t-test (parametric); or Mann-Whitney test (non-parametric) |
| Mean number of hospital admissions (inpatient palliative care) | Numerical | mean | Baseline<br>Wk12<br>Wk18<br>Wk24 | t-test (parametric); or Mann-Whitney test (non-parametric) |
| Mean number of medical consultations | Numerical | mean | Baseline<br>Wk12<br>Wk18<br>Wk24 | t-test (parametric); or Mann-Whitney test (non-parametric) |
| Mean number of medications | Numerical | mean | Baseline<br>Wk12<br>Wk18<br>Wk24 | t-test (parametric); or Mann-Whitney test (non-parametric) |
| Involvement of allied health (physiotherapist, occupational therapist, dietitian, social worker) | Categorical dichotomous (yes, no) | 1. mean<br>2. time to referral<br>3. time to review | Baseline<br>Wk12<br>Wk18<br>Wk24<br>Longitudinal | 1. t-test (parametric); or Mann-Whitney test (non-parametric)<br>2. time-to-event analysis |
| Referrals to oncology rehabilitation program | Categorical dichotomous (yes, no) | 1. mean<br>2. time to referral | Baseline<br>Wk12<br>Wk18<br>Wk24<br>Longitudinal | 1. t-test (parametric); or Mann-Whitney test (non-parametric)<br>2. time-to-event analysis |
| Participation in oncology rehabilitation program | Categorical dichotomous (yes, no) | 1. mean<br>2. time to participation | Baseline<br>Wk12 | 1. t-test (parametric); or |

| | | | | |
|---|---|---|---|---|
| | | | Wk18<br>Wk24<br>Longitudinal | Mann-Whitney test (non-parametric)<br>2. time-to-event analysis |
| Referrals to MyAgedCare | Categorical dichotomous (yes, no) | 1. mean<br>2. time to referral | Baseline<br>Wk12<br>Wk18<br>Wk24<br>Longitudinal | 1. t-test (parametric); or Mann-Whitney test (non-parametric)<br>2. time-to-event analysis |
| Seen by Aged Care Assessment Service | Categorical dichotomous (yes, no) | 1. mean<br>2. time to review | Baseline<br>Wk12<br>Wk18<br>Wk24<br>Longitudinal | 1. t-test (parametric); or Mann-Whitney test (non-parametric)<br>2. time-to-event analysis |
| Referrals to Community Palliative Care | Categorical dichotomous (yes, no) | 1. mean<br>2. time to referral | Baseline<br>Wk12<br>Wk18<br>Wk24<br>Longitudinal | 1. t-test (parametric); or Mann-Whitney test (non-parametric)<br>2. time-to-event analysis |
| Seen by Community Palliative Care | Categorical dichotomous (yes, no) | 1. mean<br>2. time to review | Baseline<br>Wk12<br>Wk18<br>Wk24<br>Longitudinal | 1. t-test (parametric); or Mann-Whitney test (non-parametric)<br>2. time-to-event analysis |
| **Institutionalisation** | | | | |
| Institutionalisation (residential care or supported residential services) | Categorical dichotomous (yes, no) | 1. yes vs no<br>2. time to institutionalisation | Baseline<br>Wk12<br>Wk24<br>Longitudinal | 1. Contingency table analysis<br>2. time-to-event analysis |
| Social situation | → Categorical ordinal (fully independent, low, high)<br>→ Categorical dichotomous (fully independent, assisted) | 1. yes vs no<br>2. time to dependence | Baseline<br>Wk12<br>Wk24<br>Longitudinal | 1. Contingency table analysis<br>2. time-to-event analysis |

## 3.5.3. Subgroup Analyses

In addition to the analysis of the overall study population, subgroup analyses will be conducted in the following subgroups: i) palliative-intent treatment subgroup; and ii) adjuvant/curative-intent treatment subgroup.

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