Trials

STUDY PROTOCOL

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Implementing palliative care in hepatocellular carcinoma ambulatory clinics—study protocol for Accelerated translational research in PRImary liver CAncer (APRICA) randomised controlled palliative care trial

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Abstract

Background Integration of symptom and palliative care for people with advanced cancer is established in many tumour types, but its role in people with hepatocellular carcinoma (HCC) has not been clearly defined. This study aims to evaluate the clinical and cost effectiveness of an intervention involving a suite of strategies designed to assess and treat palliative care symptoms and needs in adult outpatients with HCC attending four New South Wales (NSW) metropolitan tertiary hospitals.

Methods This trial will use a pragmatic cluster-based randomised-controlled design, with ambulatory HCC services as the clusters. HCC patients will be recruited if they have Barcelona Clinical Liver Cancer (BCLC) stage A disease with active tumour or a current or prior diagnosis of BCLC stage B or C disease regardless of tumour activity. Patients with BCLC stage D disease will be excluded as palliative care is the standard of care (SOC) in this group. Cluster sites will be randomised to the study intervention or control where patients are managed according to SOC. All participants will complete the liver-specific Edmonton Symptom Assessment Scale (ESAS) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire at regular ambulatory clinic appointments. At intervention sites, patients scoring ≥ 5 on any liver-specific ESAS symptom will be referred to palliative care physicians for consultation. The primary clinical outcome will be improvement in all symptoms scored ≥ 5 on the liver-specific ESAS by 50% within 3 months and the primary implementation outcome will recording the liver-specific ESAS

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in ≥ 80% of all participants attending clinic appointments. Caregivers of patients enrolled in the trial will be invited to perform Carer Support Needs Assessment Tool at each appointment.

Discussion This trial will inform if earlier palliative care involvement significantly reduces the symptom burden associated with HCC. If found to be effective, earlier implementation of palliative care consultation should be included in HCC treatment guidelines.

Trial registration ACTRN12623000010695. Registered on September 1, 2023.

Background

Hepatocellular carcinoma (HCC) is the most common primary liver cancer [1, 2]. In Australia, it is the fifth most common cause of cancer death in men and seventh in women [1]. The incidence and mortality burden of HCC in Australia is increasing [2]. Sixty percent of cases are attributable to viral hepatitis which disproportionally affects individuals who are culturally and linguistically diverse, Aboriginal and Torres Strait Islander people, and those from disadvantaged backgrounds [2]. Compared to other cancers, primary liver cancer is often diagnosed at a late stage. HCC management is complex and optimal treatment decisions require consideration of a range of clinical, tumour and liver related factors [1]. Currently, the 5-year survival rate for primary HCC is 18% [1, 2].

Palliative and supportive care is the speciality of medicine that utilises interdisciplinary teams to improve symptom management, quality of life (QOL), future care planning, and carer preparedness and support [3]. Palliative care has been integrated into models of care for several end-stage conditions, including advanced malignancy, chronic kidney failure, and congestive cardiac failure [4, 5]. For example, in people with lung cancer, this approach has established outcomes in advanced cancer where utilisation of palliative care services increases survival, reduces hospital admissions, and improves the QOL [5]. A recent meta-analysis which studied the effects of early palliative care for people with advanced cancer found those who received early palliative care reported better symptom control, improved quality of life and mood parameters, as well as improved survival and a higher probability of dying at home [6]. The majority of palliative care interventions are triggered by a specific timepoint in a patient's cancer trajectory, marked either by diagnosis, stage, and/or by patient reported outcomes that show unmet needs.

Symptom management has a critical role in palliative care interventions. Several systematic reviews have found computerised symptom screening in cancer settings to be feasible, acceptable and contribute to improved processes of care such as doctor-patient communication and referrals [7, 8]. Patient reported symptom screening (with most studies collecting these electronically) leads to improvements in QOL, symptom severity, improved survival, and reduced hospitalisation and emergency department presentations [9]. When uncontrolled symptoms are identified, it has been shown that a clear pathway of care optimises symptom management [10].

International hepatology guidelines for the management of HCC include recommendations for palliative care after all active measures have been exhausted, which clinical experience suggests is often too late to provide meaningful benefit to patients and their carers and leaves many supportive care needs unmet [11–15]. It also does little to address supportive care needs of those receiving palliative treatments for hepatocellular carcinoma including locoregional and systemic therapies, increasingly being possible treatments offered at various stages of the disease [16]. This guidance is predominantly based on consensus opinion, with little known about the unmet supportive care and decision-making needs longitudinally over time for individuals with HCC. The literature also does not provide guidance on a specific approach or timing for an integrated palliative care pathway for HCC that addresses the twin challenges of their cancer and, frequently, liver failure. At this time, international clinical guidelines for the management of HCC broadly suggest palliative care should be considered [17–19].

The effects of early palliative care referral in HCC patients have not been well studied. Therefore, we have designed this trial to implement early referral to palliative care based upon symptom measures to assess a number of key patient focused outcomes.

Significance

As people with HCC are living longer, addressing symptoms is ever more critical in optimising functioning and QOL, as unrelieved symptoms interfere in all aspects of life—mobility, working, relationships, sleep, and life enjoyment. This study will look to explore the impact of earlier palliative care referral in HCC patients based upon symptom measures compared with current standard of practice.

Methods

Study design

This prospective study is a pragmatic cluster-based randomised controlled design clinical trial with four

Australian tertiary ambulatory HCC services as the clusters (Fig. 1). The rationale for the choice of this design is to show clear differences between early referral to palliative and supportive care and standard HCC care with on-demand palliative care referral aiming for superiority of the intervention over standard care. It also avoids site contamination from observed outcomes due to the lack of ability to blind patients and clinicians to the intervention. Human research ethics approval was granted by the South Western Sydney Local Health District Health Research Ethics Committee (SWSLHD HREC). The trial was retrospectively registered on the Australian and New Zealand Clinical Trials Registry on 09/01/2023 with registration number ACTRN12623000010695. This protocol complies with reporting requirements outlined in the cluster randomised controlled trial extension of the Consolidated Standards of Reporting Trials (CONSORT) [20]. The plan is to recruit a minimum of 386 eligible participants who are assigned to intervention or control based on the location of their regular HCC ambulatory clinic appointments. Participants will undergo repeated follow-up for the trial period of 5 years.

Participants at these four sites will undergo liver-specific Edmonton Symptom Assessment Scale (ESAS) through waiver of consent as this questionnaire will be introduced as standard of care. Participants will be automatically offered further questionnaires including EORTC QLQ-C30 and CSNAT through verbal consent. Participants will be given the option of receiving emailed liver-specific ESAS questionnaires prior to subsequent ambulatory HCC clinic appointments. Participants at intervention sites who receive a liver-specific ESAS score of ≥ 5 on at least one of the ten symptoms in the questionnaire will be invited to undertake referral to a palliative care physician for consultation for further symptom, quality of life, and carer assessment. Clinicians at the control sites are blinded to the outcomes of all patient and carer questionnaires.

As this study involves a complex intervention with multiple interacting components, an implementation evaluation alongside the RCT will assess fidelity of the intervention as implemented in the four sites, processes of care, adaptations, and barriers and enablers of implementation whilst taking into account the contextual factors at each site. This will inform further refinement and tailoring of the intervention to different settings and contexts. The implementation evaluation is guided by the Consolidated Framework for Implementation Research (CIFR) [21].

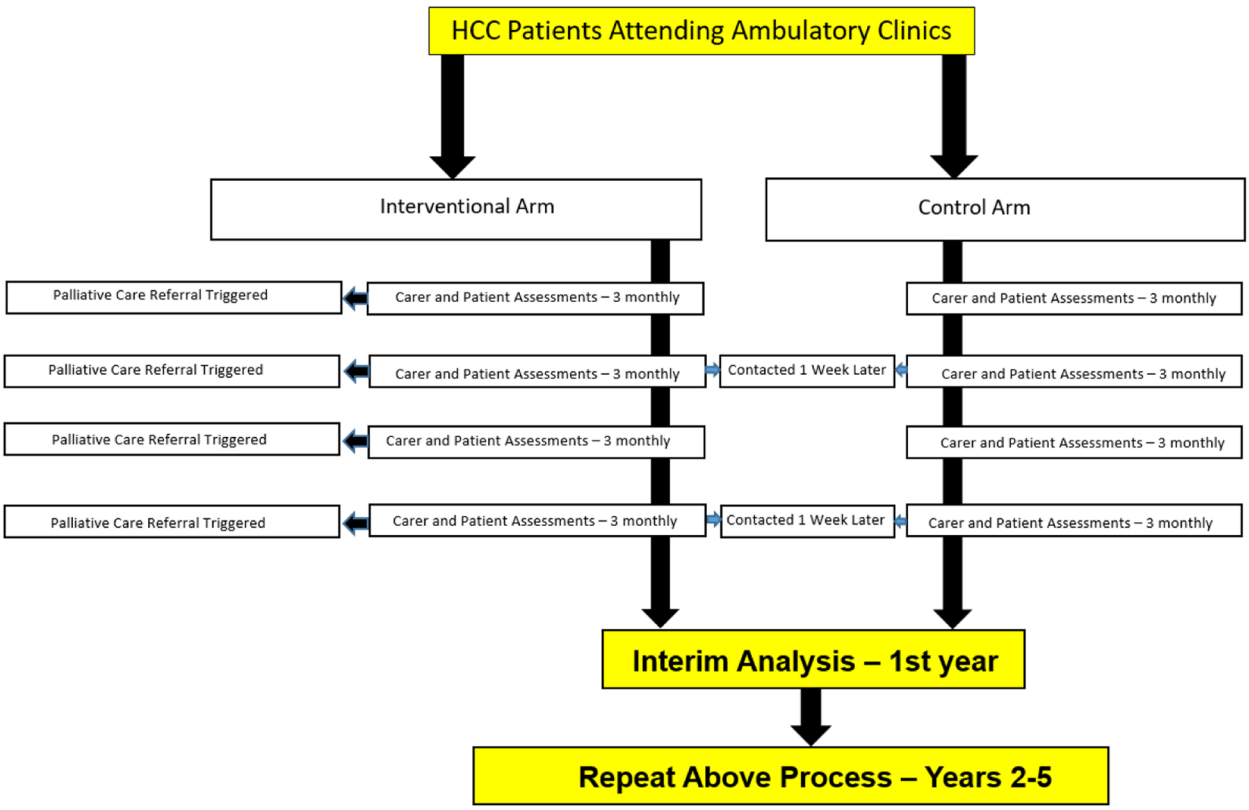

Fig. 1 Flow chart for HCC patients attending ambulatory clinics

Recruitment and eligibility criteria

Enrolment will be completed within 5 years (from the beginning of recruitment of the first patient). Site research staff will screen all outpatients attending HCC ambulatory clinic appointments according to the inclusion and exclusion criteria. Site staff will recruit and consent patients for this study. All patients attending the four sites will participate in initial questionnaires and baseline demographic information through waiver of consent as liver-specific ESAS will be introduced as standard of care. All additional measures including referral to palliative care for intervention will be obtained through verbal consent.

The inclusion criteria are patients: (1) attending a participating HCC and palliative care centre as an outpatient during the study period; (2) Barcelona Clinical Liver Cancer (BCLC) stage A disease with active tumour; (3) current or prior diagnosis of BCLC stage B or C disease regardless of tumour activity; (4) age > 18 years; and (5) be able to complete a 0–10 liver-specific ESAS (in English, simplified Chinese, Arabic, Vietnamese, or Greek).

The exclusion criteria are patients: (1) with BCLC stage 0 or D disease; (2) with BCLC stage A disease with no active HCC confirmed on recent imaging; (3) who have been referred to palliative care prior to enrolment; (4) who opt-out of completing the liver-specific ESAS and needs assessment; (5) who participate at another centre taking part in the trial; (6) documented as having cognitive impairment that would preclude capacity to give informed consent; and (7) patients with a history of liver transplantation.

Participants will be asked to identify a primary caregiver who will be invited to complete a Carer Support Needs Assessment Tool (CSNAT).

Inclusion criteria for carers are those: (1) identified by a patient who has completed the liver-specific ESAS as providing the patient with substantial emotional and practical support in an unpaid capacity and (2) with spoken and written English proficiency sufficient to complete the CSNAT.

Enrolment for the study began on July 28, 2022.

Outcomes

Primary outcomes

The primary clinical outcome is improvement of palliative care symptoms, as defined by a reduction in all liver-specific ESAS total symptom score ≥ 5 (Minimally Important Clinical Difference for Improvement) by 50% within 3 months of consultation with the palliative care clinician. The primary implementation outcome will assess adherence rate, with a target of 80% or more of all patients who meet the patient eligibility having a liver-specific ESAS performed at all designated timepoint clinic attendances.

Secondary outcomes

Secondary outcomes for this study include improvement in patient quality of life, palliative care referral, input from palliative care consultation, mortality difference, hospital admission for liver-specific cause, hospital admission for non-liver-specific cause, cost-effectiveness, structural and process measures.

Interventions

The intervention is referral to a palliative care physician for consultation and management of symptoms, quality of life, and caregiver support at active sites based upon liver-specific ESAS results. Control sites will not be given access to the liver-specific ESAS results and will refer to palliative care physician at the current SOC. Referrals at the intervention sites will be screened by treating clinicians prior to referral to assess if referral is appropriate. Management of symptoms will be based on palliative care physician assessment and management, which will be recorded. Pharmacotherapy guidance will be provided to palliative care physicians (developed with their input) at intervention sites to provide some standardised principles for symptom management.

Baseline data collection

Baseline demographic data regarding the patients age, sex, availability of unpaid carer, postcode, country of birth, language spoken at home, and Indigenous status will be recorded. Baseline cancer data will include time since diagnosis, previous treatment, tumour stage (utilising BCLC coding), Child Pugh Status, model for end-stage liver disease-sodium (MELD-Na) score, current treatment, underlying liver disease (if present), and time since diagnosis of underlying liver disease (if present). Baseline comorbidities will be recorded if present. Baseline performance status involving Karnofsky Performance Status (KPS) or Australia-modified Karnofsky Performance Status (AKPS), and Eastern Oncology Cooperative Group (ECOG) Performance Status will be recorded (Tables 1 and 2).

Follow-up

All participants will be followed by their clinician at each regularly scheduled HCC ambulatory clinic appointment. Trial participants will continue their usual treatment regimen in all respects other than those prescribed for palliative care symptom treatments in the intervention period.

Table 1 Patient and carer measures

	Screening	Following consent	Months 3, 6, 9, 12	Yearly and exit (at 5 years or time of death)
Medical file review				
DOB	*			
Gender	*			
Language spoken at home	*			
Aboriginal or Torres Strait Islander status	*			
Diagnoses (cancer and other)	*			
AKPS/ECOG	*			
Patient measures				
Liver ESAS	*		*	*
EORTC		*	*	*
Availability of primary carer		*		
Palliative assessment and management audit				*
Carer measure				
CSNAT		*	*	

AKPS/ECOG Australia-modified Karnofsky Performance Status/Eastern Cooperative Oncology Group, *CSNAT* Carer Support Needs Assessment Tool, *DOB* date of birth, *EORTC* European Organisation for Research and Treatment of Cancer, *ESAS* Edmonton Symptom Assessment Score, * denotes information collected at this event

Table 2 Data collection sources

Task title	Output(s)	Deliverables	Performance indicators
Assessing baseline palliative care needs—patients	EORTC, liver-specific ESAS	Performed questionnaires	Initial performance of questionnaires
Assessing baseline palliative care needs—carers	CSNAT	Performed questionnaires	Initial performance of questionnaires
Ongoing palliative care needs—patients	EORTC, liver-specific ESAS	Performed questionnaires every 3 months	Symptoms reviewed every 6 months, % change in baseline in intervention/non-intervention
Ongoing palliative care needs—carers	CSNAT	Performed questionnaires every 3 months	Need reviewed every 6 months, % change in baseline in intervention/non-intervention
Referrals to palliative care	Referrals from ambulatory care HCC clinic	Number of referrals	Referral numbers/total HCC numbers
Palliative care output	Treatments initiated	Type of treatment initiated	Reviewed every 6 months
Admission to hospital	ED admission to hospital	Review reason for admission	Number of ED admissions Reason for ED admission
Liver cancer treatments (locoregional/systemic treatment)	Types of liver cancer treatments		Number of treatments for patients
Mortality	Mortality	Timing of mortality after enrolment	Mortality rate in intervention versus control group every 6 months
Liver specific comorbidities	Liver specific comorbidities	Episodes of hepatic encephalopathy Episodes of UGI bleeding Episodes of SBP	Assessing complication rate in palliative care versus non-palliative care group every 6 months
Treatment specific comorbidities	Treatment specific comorbidities	Immunotherapy side effects Systemic treatment side effects Locoregional therapy side effects	Assessing side effect profiles between groups every 6 months
Benefit to patients and carers	Follow-up surveys every 6 months		Assessing improvements in symptoms and sense of control over palliative care symptoms

CSNAT Carer Support Needs Assessment Tool, *ED* emergency department, *EORTC* European Organisation for Research and Treatment of Cancer, *ESAS* Edmonton Symptom Assessment Score, *HCC* hepatocellular carcinoma, *SBP* spontaneous bacterial peritonitis, *UGI* upper gastrointestinal

Sample size

To assess the appropriate study sample size and compute study power, we simulated previously performed early palliative care interventions in patients with different types of cancer [4, 5]. Previous utilisations of early palliative care referral have shown up to a 20% difference in mortality at the end of 1 year [5]. We have utilised mortality benefit as a sample size and power calculation, due to the lack of literature surrounding the use of liver-specific ESAS in HCC, and the symptom improvement associated with palliative care in this setting. Utilising a more modest 15% difference in mortality at the end of 1 year, with current mortality sitting at 49%, with two sided dichotomous groups with a type I/II error rate of 0.05 and powered to 80%, the total sample size needed for the primary objective is 386 (with 193 in the intervention group and 193 in the control group). There are around 1000 new diagnoses of HCC per year in New South Wales (NSW), and these four tertiary hospitals cover the main referral pathways in metropolitan Sydney. We will be over sampling the population which will allow us to pick up smaller differences in mortality and address all secondary objectives.

Using a cluster-based clinical trial design with fixed clusters with a significance level of 0.05, beta of 0.2, intercluster correlation coefficient of 0.03 with a binary outcome, the calculated sample size for each cluster is 130 for a power of 0.8. Utilising these two calculated measures, this allows for a patient recruitment of between 193 and 260 patients in both intervention and control arms (386 to 520 patients in total sample size) to allow for sample size to be appropriately powered for the primary objectives. A retrospective analysis of 12-month mortality for new diagnosis of HCC for the prior 2 years for each centre will be conducted to assess baseline as part of the study analysis. These numbers have been reviewed by a statistician and are appropriate for this study design.

Randomisation and blinding

Allocation of intervention vs. control will be controlled at site level as per cluster-based trial design. There will be no individual patient randomisation occurring. The nature of the intervention in this study renders blinding of health professionals impractical. Information and consent forms for patients will provide only general information about the aims of the study (i.e. that it will compare different approaches to palliative care referral and management rather than the specifics of the design and intervention). Health professionals will be asked not to discuss the study design or current arm at their centre with patients and carers. Previous experience of cluster randomised controlled trials by the current team members suggests that attempts to blind research assistants collecting data will be impractical. Instead, attention will be paid to standardisation of data collection as ways to limit the potential for bias. Personnel conducting analyses will be blinded to centre allocation.

Qualitative research

Qualitative studies will be conducted alongside the trial to inform implementation evaluation. We will conduct semi-structured interviews with people living with HCC and their carers regarding their experience and views of integrating palliative care in their clinical care. Purposive sampling will be used to ensure we capture the diverse populations this condition affects. Additionally, we will conduct focus groups with HCC care providers to identify barriers and facilitators to embedding palliative/supportive care management within their current service provision.

Semi-structured interview schedules will include guiding questions and prompts to elicit information about experiences, barriers, and enablers encountered whilst implementing the intervention (staff at the four sites) or using the intervention (patients and carers at the 4 sites). We will initially undertake interviews with 4 patients at each of the 4 sites to better understand the enablers and barriers to palliative and supportive care management in HCC. All interviews will be recorded, transcribed verbatim and thematically analysed according to the methods described by Braun [22]. A hybrid inductive-deductive analysis approach will be used, where themes based on specific questions will be consolidated, whilst at the same time identifying emergent themes from the qualitative data. Additional interviews with patients will be undertaken if the themes are broadly divergent after four patients had been interviewed until no new themes emerge with up to 10 patients and carers being interviewed at each site. In addition, we will undertake interviews with carers of patients with HCC patients to understand their experiences of care before the introduction of the intervention. Interviews with healthcare professionals that work with individuals with hepatocellular carcinoma, both in the liver service and in palliative care will also be undertaken to understand the barriers, enablers, and needed adaptations when implementing the intervention. Separate interview schedules will be developed for the healthcare professionals and the thematic analysis will be undertaken as described above.

Data collection and management

Confidential information will be strictly maintained throughout the clinical trial. Study data were collected and managed using REDCap electronic data capture tools hosted at Office of Health and Medical Research

server [23, 24]. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources. As the database will be set up under the OHMR licence, NSW Health sites are permitted to hold identifiable information within REDCap databases. Patient data for each site will only be accessible to password-holding personnel at that site. Investigators at the coordinating site (CG, JG, RB, MA) will have access to data from all study sites, to enable database management and data analyses. Identifiable information will be entered for patients from each study site using data access groups and will be used to generate questionnaires for each participant. Only study staff at each specific site will have access to the data collected at their local health district and will only be accessible by password. Investigators at the coordinating site will have access to data from all study sites, to enable data management and data analysis. A designated staff member at each site will enter baseline screening data into the REDCap database. Electronic data will be stored on password-protected computers in secure offices at the coordinating site. Study sites will likewise store baseline screening electronic data generated at their site on password-protected computers in secure offices. All study files will be stored in accordance with Good Clinical Practice guidelines.

Quality control

The trial will be performed by Liverpool Hospital (Hepatology and Palliative Care), Royal Prince Alfred Hospital (Hepatology), St George Hospital (Hepatology and Palliative Care), and Westmead Hospital (Hepatology and coordinating site). The trial steering committee consists of the lead clinical research team at all four sites. The research team consists of a chief principal investigator for the APRICA program, chief principal investigator for APRICA-Palliative Care Trial, four site principal investigators, a study coordinator, two palliative care physicians at intervention sites, and lead investigator who is responsible for data and trial management. The research team meets monthly to assess the progress and to work out logistical issues. A statistician was involved in the design of the trial and will be consulted on statistical issues throughout the study. Researchers at each of the four sites will collect general patient information.

The data monitoring committee (DMC) consists of coordinating principal investigator for the APRICA program, coordinating principal investigator for APRICA-Palliative Care Trial, study coordinator, and lead investigator. The DMC will meet weekly to assess the progress of the clinical trial, safety data, and logistical issues. They will conduct yearly interim data analysis in conjunction with the statistician to assess stopping rules. The results will be published in relevant publications for public access.

Statistical analysis

For the main analysis, linear mixed models will be used to model the outcomes of interest, whilst accounting for the clustering and longitudinal design. Although designed for the analysis of continuous outcomes, previously conducted computer simulations confirmed that this approach will be suitable for the liver-specific ESAS and other scores that are measured on a ten-point scale. The linear mixed modelling framework is very flexible. For example, it will allow for testing whether treatment effects diminish over time. It will also allow the incorporation of additional covariates of interest, for instance patient age, sex, ethnicity, and other factors related to their type of disease; and inclusion of covariates that reflect characteristics of the study centres. Statistical analysis will be performed using the IBM Statistical Package for Social Science (SPSS, Armonk, NY, USA). For secondary patient outcomes, analyses will be repeated for patients with clinically significant (≥ 2) and moderate-severe (≥ 5) palliative care symptoms on the liver-specific ESAS.

Qualitative analysis

Qualitative research will be analysed through thematic analysis utilising grounded theory.

Cost effectiveness analysis

The economic evaluation involves three steps:

1. A determination of the incremental effectiveness, which is measured as the additional benefits associated with the intervention relative to no intervention, which in this case is palliative care.
2. A determination of the incremental costs, that is, the difference in costs between intervention and no intervention.
3. A determination of the incremental cost-effectiveness ratio (ICER) at the end of 12 months, calculated using the following ratio.

$$ICER = \frac{Cost_{Intervention} - Cost_{No\ intervention}}{Effectiveness_{Intervention} - Effectiveness_{No\ Intervention}}$$

Quality of life data collected at 0, 3, 6, 9, and 12 months will be used to conduct a modelled cost-utility analysis. As economic data may be skewed, confidence intervals will be estimated with bootstrap methods. Sensitivity analysis will examine the effect of assumptions and determine which cost component drives the results.

Reports of adverse events

Clinical staff and managers at participating centres will be required to report to the project team any adverse incidents that they believe may be related to the project intervention or study procedures. After the initial report, investigators are required to follow-up each incident and provide further information both to the coordinating centre (Storr Liver Centre) and the approving HREC, if required. All incidents reported as ongoing are to be reviewed at subsequent visits or appointments in order to report progress and resolution.

All events are to be followed until:

- Resolution.
- The event can be explained.
- A participant involved is lost to follow-up.
- A participant involved dies.

Reports are to contain details of follow-up investigations, result reports or reports from other consultations, and are to be updated in a report to the coordinating centre and the approving HREC. The study will be stopped if reporting of incidents indicates that review of the study protocol is required or if new literature indicates findings that answer the research questions.

Trial status

Version 1.8 of study protocol currently in use from May 15, 2023. Enrolment for the study began on July 28, 2022, and enrolment completion date is expected to be July 28, 2027.

Discussion

HCC carries 51% and 18% survival rates at 1 and 5 years, respectively [1]. Currently, other malignancies have clear palliative care pathways integrated into their treatment algorithms as they are principally managed by oncologists [6]. There is a deficit in the knowledge regarding palliative care integration into HCC patient treatment pathways [15, 17–19]. It is essential that we gather this information to help determine the best way to provide this integral aspect into standard HCC care. This project is not only essential for HCC patients in our local health districts, but dissemination of the results will inform palliative care integration across Australia and internationally. The unique aspects of the design of this trial are that it is pragmatic in nature (to be able to be implemented routinely), whilst providing an ability to evaluate effectiveness and longitudinal symptoms and unmet needs utilising validated measures in HCC. Additionally, the trial will perform an economic analysis of the intervention, whilst also capturing any survival benefits from the intervention.

Subgroups of people with HCC who stand to benefit disproportionately from intervention are patients with limited English and health literacy [1]. Australian research suggests cancer patients from non-English speaking backgrounds may have greater unmet needs arising from problems with communicating with health professionals and lack of knowledge of the health system [25]. In the proposed project, tools for screening palliative care symptoms will be translated into community languages to ensure that medical teams are made aware when patients have symptoms without relying on verbal communication.

The proposed project is strategic at a healthcare systems level because it will: (1) facilitate coordination between different sectors involved in caring for people in the community with HCC. Problems with coordination have been consistently emphasised by research looking at barriers and facilitators to cancer care; (2) ease the transition between supportive cancer care and palliative care for people with incurable cancer; (3) take a coordinated approach to overcoming barriers to implementation at systems, provider, and patient levels; and (4) ensure that care is firmly centred on the patient and his/her family whilst simultaneously ensuring standardised best practice evidence-based care.

The patient-held resources to be evaluated in this project will empower patients and carers to self-manage palliative care symptoms in the community with the support of health professionals as needed. This model is the mainstay of management for symptoms from other chronic diseases like arthritis, diabetes, and other forms of cancer; now is a strategic time to make the same transition for HCC. The proposed intervention has inbuilt strategies for centres to monitor performance and act on gaps in care and includes the required educational and systems supports to facilitate change.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08603-x.

Additional file 1: SPIRIT 2020 checklist.

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Authors' contributions
The manuscript was written by CG, the lead investigator, and reviewed with inputs from JG, RB, and MA. All authors read and approved the final manuscript. MA, JG, GM, AZ, SS, and ML are the principal investigators and conceived the study with CG and RB. The following contributed to development of study methodology and data collection: CG, ADB, RB, YZ, FSB, KC, GM, AZ, SS, ML, CS, SG, JM, JMD, LS, KL, SG, SD, TDH, ZQ, MA, and JG.

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Data availability
The datasets utilised and examined in this study can be obtained from the principal investigator (Jacob George) upon reasonable request.

Declarations

Ethics approval and consent to participate
This study has been approved by South Western Sydney Local Health District Human Research Ethics Committee (2022/ETH00385). Each patient will provide informed consent prior to commencement of any procedures specific to the study.

Consent for publication
Not applicable—no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent form are available from the corresponding author on request.

Competing interests
The authors declare no competing interests.

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