ECOS Application Form

ECOS Ref No.: 2025-0194
Form Ref: 2025-0194-APP1
Initial Study Review Category: Expedited
Form Outcome: Approved
PI/Site-PI: Prof Koh Gerald (NUS - Saw Swee Hock School of Public Health), Dr Lim Mervyn (National University Hospital)
Study Title: Navigating Advanced Illness Goals And Treatment with digital Engagement (NAVIGATE)

Section A: Study Title

A1. Please enter the Study Title for this Study.

Navigating Advanced Illness Goals And Treatment with digital Engagement (NAVIGATE)

Section B: Submission Board, Study Site, Study Investigator and Conflict of Interest

B1. Submission IRB and Board

B1. (a) The reviewing IRB would be:

NHG DSRB

B1. (b) Please select the board.

Domain F1

B1. (c) (i) Primary Specialty

Others

B1. (c) (ii) Primary Sub-specialty

B1. (c) (iii) Secondary Specialty

B1. (c) (iv) Secondary Sub-specialty

B1. (d) Has the study been submitted to another IRB?

○ Yes
◉ No

B1. (e) Has the application been previously rejected by any IRB?

○ Yes
◉ No

B2. Study Site and Study Investigator

B2 (a) Please select the study sites and investigator.

Study Site

Study Site	Location*	Endorsement needed
NUS - Saw Swee Hock School of Public Health	NUS - Saw Swee Hock School of Public Health	Yes
National University Hospital	NUH	Yes

Study investigator

Study Site	Name	Study Role	Designation	Department	Institution	Profile and Minimum Training	Conflict of Interest
National University Hospital	Ms Siena Ong (NUH)	Co-I	Clinical Research Coordinator	Surgery	National University Hospital	Complete	No
National University Hospital	Dr Lim Mervyn	Site-PI	Senior Resident	Surgery	National University Hospital	Complete	No
National University Hospital	Dr Chan Noreen	Co-I	Associate Professor	Medicine	NUS - Yong Loo Lin School of Medicine	Complete	No
NUS - Saw Swee Hock School of Public Health	Mr Huynh Vinh Anh	Co-I	Research Assistant	NUS - Saw Swee Hock School of Public Health	NUS - Saw Swee Hock School of Public Health	Complete	No
NUS - Saw Swee Hock School of Public Health	Dr Foong Pin Sym	Co-I	Research Fellow	NUS - Saw Swee Hock School of Public Health	NUS - Saw Swee Hock School of Public Health	Complete	No
NUS - Saw Swee Hock School of Public Health	Prof Koh Gerald	PI	Professor	NUS - Saw Swee Hock School of Public Health	NUS - Saw Swee Hock School of Public Health	Complete	No

B2. (b) Study Sites (For Information Only)*

Section C: Study Funding Information

C1. Please provide information regarding the study's funding source or sponsor information.

○ (a) Department Fund or No funding is required for this study to be carried out

◉ (b) Grant

○ (c) Pharmaceutical/ Industry Sponsored

C1. (b) (i) Name of Grant Agency:

Ministry of Health

C1. (b) (ii) Grant Holder:

Prof Dr. Gerald Koh Choon Huat

C1. (b) (iii) Grant Amount Applied for:

3.2M

C1. (b) (iv) Has the grant been approved?

◉ Yes

○ No

C1. (b) (iv) Attachment

LOA_CareEco21-0030_Gerald Koh_NUS (revised).pdf [03 Feb 25 16:24:40]

C1. (b) (v) Is the study's initiation dependent on grant approval?

○ Yes

◉ No

C1. (b) (v) (I) Please state alternate funding:

NMRC Centre Grant Programme – Category 1

C1. (b) (vi) Grant Reference Number

CareEco21-0030

C2. Will the funding/sponsor cover all research-related costs e.g., drugs, devices, procedures, tests and visits?

◉ Yes

○ No

○ Not applicable - no research-related costs

Section D: Study Type and Nature

D1. Form Type: Please select the appropriate form for submission.

◉ Application Form
◯ Exemption Application Form

D2. Study Classification: Please determine which set of regulations would govern the study (or any part of the study).
◯ (a) Clinical Trial - Regulated by Health Products Act/ Medicines Act (HSA)
◯ (b) Human Biomedical Research - Regulated by Human Biomedical Research Act (MOH)
◯ (c) Restricted Human Biomedical Research – Regulated by Human Biomedical Research Act (MOH)
◉ (d) Others – The study is not regulated by Health Products Act/ Medicines Act (HSA) nor Human Biomedical Research Act (MOH)

D2. (d) Please justify why the study is not regulated by Health Products Act/ Medicines Act (HSA) or Human Biomedical Research Act (MOH).
The study is not an HBR as the primary objective is for education purpose.

D3. Does the study involve any of the following? Please select where applicable (more than 1 can be selected).
☑ Questionnaire/ Survey/ Interview/ Focus Group Discussion
☑ Medical Records Review
☐ Human Biological Material
☐ Recording of Study Procedures on Audiotape, Film/video, or Other Electronic Medium
☑ Use of Software or Mobile Applications
☐ Medical Device (including Telehealth Medical Device. Please refer to HSA website to determine if your product is considered Medical Device in Singapore.)
☐ Surgical / Radiotherapy Procedure
☐ Interventions/ Invasive Procedures
☐ None of the above

D4. Would the study involve recruitment?
◉ Yes
◯ No

D4. (a) Would the study involve recruitment of any of the following as research participants?
☑ Not applicable, the study does not involve vulnerable participants
☐ Pregnant Women, Foetuses & Neonates
☐ Children
☐ Prisoners
☐ Cognitive Impaired Person
☐ Other Vulnerable Population

D5. Please select the applicable type(s) of consent for the study.

☑ Consent will be obtained
☐ Waiver of documentation of consent (Verbal or Implied Consent) - This option mostly applicable for Questionnaire/ Survey/ Interview/ Focus Group Discussion
☐ Waiver of consent during emergency situation
☐ Waiver of consent
☐ Not applicable as study involves De-identified Data
☐ Consent obtained from research participants previously

Section G: Research Methodology

G1. What are the specific aims of this study?

For caregivers, the study has the following aims:
Aim 1 (primary aim): To determine whether the use of the digital intervention (Careverse) helps caregivers of seriously ill patients increase their engagement advance care planning (ACP) process, as measured by the 17-item ACP Engagement Survey- Surrogate Decision-Maker (ACP SDM 17).
Aim 2: To evaluate the intervention effect on caregivers actual ACP behavioural outcomes.
Aim 3: To evaluate other care and health outcomes related to the use of Careverse.

For patients, the study has the following aim:
Aim 4: Lastly, we aim to investigate long-term effect of Careverse on healthcare utilization by patients, with a focus on aggressive treatments.

G2. What are the hypothesis of this study? For qualitative studies, please provide the research question(s) instead.

Aim 1 (focusing on caregivers):
Our first and primary aim is to determine whether the use of the digital intervention (Careverse) helps caregivers of seriously ill patients increase their engagement advance care planning (ACP) process, as measured by the 17-item ACP Engagement Survey- Surrogate Decision-Maker (ACP SDM 17).
• Hypothesis 1 (primary): We hypothesise that as compared to caregivers in the control arm, caregivers using Careverse will report higher degree of ACP engagement, as measured by higher overall scores of ACP SDM 17.
We further hypothesise that, as compared to caregivers in the control arm, caregivers using Careverse will also report greater scores in four subdomains related to ACP engagement:
• Hypothesis 1.1: Report higher knowledge of serving as a surrogate decision-makers (knowledge and self-efficacy domain)
• Hypothesis 1.2: Be more likely to contemplate ACP conversations with patients and doctors (contemplation domain)
• Hypothesis 1.3: Be more ready to have ACP behaviours with patients and doctors (readiness domain)

Aim 2 (focusing on caregivers):
We also aim to evaluate the intervention effect on caregivers actual ACP behavioural outcomes. We hypothesise that, as compared to caregivers in the control arm, caregivers using Careverse will:
• Hypothesis 2.1: Be more likely to report having care planning conversations with patients about patients' values and care preferences

• Hypothesis 2.2: Be more likely to report having care planning conversations with doctors
• Hypothesis 2.3 Be more likely to participate in ACP conversation with ACP facilitators (together with patients).

Aim 3 (focusing on caregivers):
Our third aim is to evaluate other care and health outcomes related to the use of Careverse. We hypothesise that as compared to control participants, intervention participants will report:
• Hypothesis 3.1: Higher satisfaction with care (for both caregivers and patients)
• Hypothesis 3.2: Better relationship and communication with patients
• Hypothesis 3.3: Better quality of life (for both caregivers and patients)
• Hypothesis 3.4: Greater goals of care congruency with patients
• Hypothesis 3.5: Better bereavement outcomes among caregivers of decedents

Aim 4 (focusing on patients):
Lastly, we aim to investigate long-term effect of Careverse on healthcare utilization, with a focus on aggressive treatments. We hypothesise that as compared to control participants, intervention participants will report:
• Hypothesis 4.1: Lower usage of aggressive treatments (eg. Intubation, CPR, resuscitation)
• Hypothesis 4.2: Lower utilisation and costs of healthcare

G3. Please state concisely the importance of the research described in this application by relating the specific aims to the long term objectives.
Decision-making for end-of-life care requires a clear communication of values and goals among patients, SDMs caregivers and healthcare providers. Our project prepares family caregivers (CG) for this task with care recipients and doctors by helping caregivers contemplate and elicit values associated with end-of-life care choices. Compared to studies in the West, Asian studies suggest that CGs are more involved in decision-making among seriously ill CRs, with a higher occurrence of CR’s leaving all decision-making to their CGs. Within the local context, other intervening factors such as the involvement of doctors and/or other healthcare professionals, language barriers, and cultural taboos may also affect the way ACP decision-making is done. This project focuses on Singapore caregivers, examining how a digital intervention might be able to increase engagement in advance care planning activities through contemplation of values and choices, towards reducing caregiver stress and burden.

This trial evaluates a caregiver intervention developed in research funded by the National Medical Research Council (NMRC), which aims to create a customizable, shareable online tool to promote advanced care planning (ACP) discussions with a special focus on patient and caregiver values in multilingual Singapore. The target audience for this project are caregivers for patients in three patient groups – advanced chronic kidney disease (CKD), symptomatic intracerebral hemorrhage (SICH) in stroke, or brain tumor (glioma or brain metastases). The baseline study for user acceptability and pre-post efficacy has concluded and the results are being analysed.

G4. Please briefly describe the background to the current study proposal. Critically evaluate the existing knowledge and specifically identify the gap(s) that the proposed study is intended to fill.
In advanced stages of illnesses where curative options are no longer available, treatment decisions become increasingly influenced by patient preferences. Evaluating care options requires the patient and family to

consider their values and the tradeoffs they are willing to make. When patients could not or do not want to participate in the process, which could be due to temporary or permanent loss of decision-making capacity, the burden of making treatment decisions often fall onto caregivers as surrogate decision-makers (SDM) to make decisions on the patients' behalf. SDMs are estimated to be involved in decision-making for 50% of hospitalizations and such responsibility will become increasingly more common for patients near the end of life. [1, 2]

SDMs face significant emotional and practical demands when making decisions, as they must balance the patient's preferences, clinical recommendations, and the family's sometimes conflicting priorities.[3, 4] While most SDMs strive for honoring the patients' wishes, SDMs often find it difficult to have the conversation about patients' end-of-life (EoL) wishes and values. Furthermore, SDMs are often influenced by their own preferences, which may not be concordant with patients' values.[5] Consequently, many feel under-prepared to take up this role.[6] Several areas where greater guidance and support for surrogates were needed include better and earlier preparation for and understanding of the importance of advanced care planning (ACP), being able to initiate ACP conversations, learning and incorporating patient's values and preferences into decision-making. The study also highlights the need support SDMs in communicating with clinicians and advocating choices as well as making informed surrogate decisions. Importantly however, multiple studies suggest that open conversations about future care preferences could help in facilitating consensus.

Existing research has focused on interventions that culminates in formal documentations of ACP.[7-10] However, research has shown that both patients and caregivers preferences constantly change over the course of the disease and caregiving journey.[11] Therefore, such ACP documentation, especially when without regular revisits and updates, may be unhelpful or even detrimental to providing goal-concordant care. Additionally current interventions are often designed to be used alongside facilitators.[12]. Yet, there exists a number of barriers especially among health care providers for facilitating such conversations, most notably time and resource constraints.[13].

Therefore, to help SDMs be more prepared and ready to make crucial in-the-moment decisions, it is hence recommended that surrogates go beyond documentation and towards serious illness communication and preparation, which entails deeper and more holistic understanding the patient's values and preferences.[9]. This underscores the need for iterative, high-quality conversations between caregivers, patients, and clinicians to determine what matters most to the patient and align care decisions accordingly. This presents an opportunity for digital interventions as an alternative solution that is scalable and allows for independent use. Having access to digital tools may also allow caregivers to easily revisit and update their choices which caters to the ever-changing nature of medical preferences.

Informed by previous studies on caregiver needs, decision-making frameworks, and existing interventions, we developed a novel website addressing caregivers' needs in preparing for their roles as surrogate decision-makers. To address challenges with motivation, we placed values elicitation in the context of decision-making, followed by interactive tools that provide opportunities for practice and customization. We followed a modular approach which allows for nonlinear navigation to support caregivers at different stages of the decision-making

journey access resources they need the most, along with shareable outputs to facilitate family-based discussions.

G5. Please provide a list of relevant references and attach at least two relevant publications that support the conduct of the study. *

1. Torke, A.M., et al., Scope and outcomes of surrogate decision making among hospitalized older adults. JAMA internal medicine, 2014. 174(3): p. 370-377.
2. Coombs, M., A scoping review of family experience and need during end of life care in intensive care. Nursing Open, 2015. 2(1): p. 24-35.
3. Sullivan, A.B. and D. Miller, Who is taking care of the caregiver? Journal of patient experience, 2015. 2(1): p. 7-12.
4. Ozdemir, S., et al., Caregiver-reported roles in treatment decision making in advanced cancer and associated caregiving burden and psychological distress: a longitudinal study. Medical Decision Making, 2023. 43(2): p. 191-202.
5. Ozdemir, S., et al., Patient–Caregiver Treatment Preference Discordance and Its Association With Caregiving Burden and Esteem. Innovation in Aging, 2021. 5(3): p. igab020.
6. Bakke, B.M., et al., Surrogate decision makers need better preparation for their role: advice from experienced surrogates. Journal of Palliative Medicine, 2022. 25(6): p. 857-863.
7. Sudore, R.L., et al., Engaging diverse English-and Spanish-speaking older adults in advance care planning: the PREPARE randomized clinical trial. JAMA internal medicine, 2018. 178(12): p. 1616-1625.
8. Fried, T.R., et al., Increasing engagement in advance care planning using a behaviour change model: study protocol for the STAMP randomised controlled trials. BMJ open, 2018. 8(8): p. e025340.
9. Rosa, W.E., et al., Advance care planning in serious illness: a narrative review. Journal of pain and symptom management, 2023. 65(1): p. e63-e78.
10. Bavelaar, L., et al., The impact of the mySupport advance care planning intervention on family caregivers' perceptions of decision-making and care for nursing home residents with dementia: pretest-posttest study in six countries. Age Ageing, 2023. 52(3).
11. Malhotra, C., et al., Instability in preference for place of death among patients with symptoms of advanced heart failure. Journal of the American Medical Directors Association, 2021. 22(2): p. 349. e29-349. e34.
12. Ryu, H., et al. “You Can See the Connections”: Facilitating Visualization of Care Priorities in People Living with Multiple Chronic Health Conditions. in Proceedings of the 2023 CHI Conference on Human Factors in Computing Systems. 2023.
13. Malhotra, C. and I. Chaudhry, Barriers to advance care planning among patients with advanced serious illnesses: a national survey of health-care professionals in Singapore. Palliative & Supportive Care, 2024. 22(5): p. 978-985.

G5. Attachment

Bavelaar2023.pdf [29 May 25 16:16:59]
Bakke2022.pdf [29 May 25 16:18:15]
Ryu2023.pdf [29 May 25 16:18:59]

G6. Please provide an account of the Principal Investigator's preliminary studies and progress reports (if any) pertinent to this application.

This trial evaluates a caregiver intervention developed in research funded by the National Medical Research Council (NMRC), which aims to create a customizable, shareable online tool to promote advanced care planning (ACP) discussions with a special focus on patient and caregiver values in multilingual Singapore. The target audience for this project are caregivers for patients in three patient groups – advanced chronic kidney disease (CKD), symptomatic intracerebral hemorrhage (SICH) in stroke, or brain tumor (glioma or brain metastases). The baseline study for user acceptability and pre-post efficacy has concluded and the results are in the process of being published. In the efficacy study, we recruited active caregivers to use the website for one week, and measured the impact through pre-post surveys (n=42) and follow-up interviews (n=6). After 7-10 days of use, the participants reported significant increase in engagement with advance care planning (ACP) behaviours across knowledge, contemplation, and readiness subscales. Participants also reported reduced decisional conflict, improvements in perceptions (but not intention) towards informal ACP conversations, and willingness towards starting a formal ACP conversation.

We observed significant improvements in the overall score of SDM-17 from a baseline mean of 3.02 (SD = 2.89) to 3.44 (SD = 2.89) post-intervention, showing a mean difference of 0.42 (95% CI [0.24, 0.6], $p < 0.001$). Participants in lower baseline quartiles showed greater improvements (+0.64 for Q1 and +0.67 on Q2) than those in the higher quartiles (+0.22 for Q3 and +0.13 for Q4).

All subscales of SDM-17 showed significant improvement, with the largest in Serving as Surrogate Decision Maker (+0.52, SD = 1.87, $p <0.001$), followed by Contemplation (+0.44, SD = 1.83) and Readiness (+0.29, SD = 1.67, $p = 0.008$). The difference between subscales was significant ($F(2, 82) = 4.4543$, $p = 0.015$), with post-hoc Games-Howell tests showing that the Serving subscale improved more than both Contemplation ($p = 0.048$) and Readiness ($p = 0.058$), with no significant difference between the latter two ($p = 1.000$).

Interestingly, interviews highlighted the usefulness of the website, especially for clinician interactions, with requests for additional interactivity, resources, and applicability to real-world decisions. The results suggests that the values elicitation segments were most efficacious, although barriers to conduct ACP conversation still remained. Our current proposed study further builds upon these results to incorporate requested features e.g. peer witness videos, and examines longer-term outcomes of the developed digital tool.

G7. Discuss in detail the experimental design and procedures to be used to accomplish the specific aims of the study. To list all procedures/activities that are carried out as part of research in this study and attach documents used for the purpose of this research.

Note:

(1) If the study involves research participant's visit, please describe the procedures involved.

(2) If this study involves medical records review, please state the source of data and specify the period of data that will be extracted for review.

STUDY SCHEDULE

For patient participants: At baseline, patients who are open to participating in research study will be approached by study team member for recruitment and consent taking. They will be asked to identify and/or confirm a caregiver who will be making medical decisions on their behalf. Upon consent, participants will be administered the baseline survey. Baseline questionnaire collects information about demographic and psychological characteristics as well as other characteristics that may be strong predictors of the primary

outcome, such as prognosis awareness. No further interventions will be administered to participants other than follow-up surveys described in the following. Patient participants will be administered three (3) follow-up surveys in total over a period of six (6) months. The schedule is detailed in Section G9 and also described below. The first follow-up (T1) is conducted at 1-week after the signup to the study and involves study team member calling the participant for data collection. The second follow-up (T2) is conducted six (6) weeks and the last follow-up (T3) at six (6) months after sign up. For both T2 and T3, surveys will be conducted in-person where study team member will arrange for data collection at the clinic (if patients have scheduled clinic appointments) or at their homes (if patients do not have scheduled visits).

For caregiver participants: Upon consent, participants will be administered the baseline survey. Baseline questionnaire collects information about demographic and psychological characteristics as well as other characteristics that may be strong predictors of the primary outcome, such as cohabitant status, financial situation, caregiving duty and arrangement. Once the baseline survey is completed, NOK caregivers will be randomized into the either the control or intervention arm. After successfully signing in to their respective allocation sites (T0), participants will use and explore the tools provided, with a reminder sent to their registered email two (2) days after successful signup. The first follow-up survey data collection will be done via individualised survey link sent to the participants' registered email at 1-week after the signup (T1), with up to two (2) reminder phone calls from CRCs after every two (2) days. After completing the first follow-up survey, participants in the intervention arm will additionally receive four (4) weekly reminder emails to explore the various tools and components in Careverse.
The second follow-up survey data collection will take place at 6-week after signup (T2). The third and final follow-up survey data collection will take place at 26-week after signup (T3). Similar to the first follow-up, individualised survey links will be sent to the participants' registered email, followed by up to two (2) reminder calls from CRCs. At the second (T2) and third (T3) follow-up, CRCs will also retrieve patients' healthcare utilisation record of consented patients from the EHR. CRCs will regularly review the EHR to identify caregivers whose patient passes away after signup to administer the appropriate instruments and questionnaire in subsequent follow-ups.

STUDY DESIGN
We will use a two-arm, single-blinded study randomized controlled trial study design for this study where caregivers will be allocated to the one of the two arms (intervention or comparison arm).
(1) Control arm: Caregivers in this arm will receive a digital version of the standard advanced care planning education material prepared by Agency of Integrated Care upon randomisation.
(2) Intervention arm: Caregivers in this arm will receive access to Careverse. Careverse is a digital psychoeducational website designed to assist caregivers and patients to clarify their values, end-of-life preferences, help surrogates increase their understanding of the patient's wishes, and prepare surrogates for the role and responsibilities of being a surrogate.
Careverse includes educational materials, testimonies, and the following tools:
a. Patient Profile Tool: A tool comprising of a series of questions to create a holistic snapshot of patient. The profile created of the patient that can be shared with care providers and other family members
b. Caring for Yourself Tool: A tool to help clarify the caregivers' profile and values
c. CareCompass Tool: a tool to help caregivers to elucidate the patients and their values and goals and to communicate these values with care providers

d. Question to Ask Tool: A tool to guide caregivers to ask the right questions and voice their concerns to care providers Caregiver participants in both arms will complete the baseline and three (3) follow-up surveys.

Patient participants will not receive any study-related interventions other than follow-up surveys described above.

G7. Attachment

Control_ACP-Workbook-EN.pdf [30 May 25 10:31:45]
Intervention_Careverse app.pdf [30 May 25 11:18:44]
CareVerse_RCT_2025_-_PT_survey_-_Baseline.docx [30 May 25 14:38:32]
CareVerse_RCT_2025_-_PT_survey_-_Follow-up_3_6months.docx [30 May 25 14:38:32]
CareVerse_RCT_2025_-_PT_survey_-_Follow-up_2_2months.docx [30 May 25 14:38:32]
CareVerse_RCT_2025_-_PT_survey_-_Follow-up_1_1week.docx [30 May 25 14:38:32]
Careverse_RCT_2025_-_CG_survey_-_Follow-up_3_6months_IRB_V2.docx [10 Jul 25 12:20:54]
Careverse_RCT_2025_-_CG_survey_-_Follow-up_2_2months_IRB_V2.docx [10 Jul 25 12:20:55]
Careverse_RCT_2025_-_CG_survey_-_Follow-up_1_1week_IRB_V2.docx [10 Jul 25 12:20:55]
Careverse_RCT_2025_-_CG_survey_-_Baseline_IRB_V2.docx [10 Jul 25 14:48:38]

G8. Please list all activities that are performed for routine diagnostic or standard medical treatment as part of the research participant's standard care.

For caregivers, there are no routine diagnostic or standard medical treatment associated with surrogate decision-making. There is no usual care for caregivers.

For patients, usual care is unaffected by the study design. We are not manipulating any of the usual care as prescribed by the clinician in charge. Instead, we only conduct observational measurements during the course of the study.
The standard care practice for each sub-group of patients in our study is as follows:
- For symptomatic intracerebral hemorrhage (SICH) stroke patients: standard care care focuses on rapid diagnosis through CT imaging, immediate blood pressure control (typically targeting systolic BP ≤140 mmHg), and reversal of any anticoagulation to minimize further bleeding. Patients are closely monitored in stroke units or ICUs, where multidisciplinary teams manage acute care, prevent complications, and initiate early rehabilitation once stable. Neurosurgical intervention may be considered in selected cases, such as large or accessible hematomas or worsening neurological status. Our recruitment begins after the active phase of treatment, when the patient is already stabilised.
- For glioma patients: the standard care sequence for high-grade gliomas, such as glioblastoma, could include maximal safe surgical resection, followed by concurrent radiotherapy and chemotherapy with temozolomide. Alternative chemotherapy regimens like PCV (procarbazine, lomustine, and vincristine) may also be considered by the clinicians. Our recruitment begins after the active phase of treatment, when the patient is already stabilised.
- For patients with Brain Metastases: management of depends on factors like the number of lesions, their size and location, the patient's overall health, and the status of systemic disease. Treatment options could include surgical resection for accessible lesions causing significant symptoms, stereotactic radiosurgery (SRS) for

patients with a limited number of brain metastases, and whole-brain radiotherapy (WBRT) for multiple lesions. Systemic therapies, including targeted therapies and immunotherapies, are also employed based on the primary cancer type and molecular characteristics.Our recruitment begins after the active phase of treatment, when the patient is already stabilised.

- For Patients with CKD Stage 4 and 5: standard care could involve a multidisciplinary approach focused on slowing disease progression, managing complications, and preparing for renal replacement therapy (RRT) when needed. Patients may receive tailored dietary advice (e.g., low protein and sodium), medication adjustments, and close monitoring for complications such as anemia, fluid overload, metabolic acidosis, and mineral imbalances. Our recruitment begins after the active phase of treatment, when the patient is already stabilised.

G9. Please state how long will each research participants will be expected to be directly involved (from screening procedures till completion of follow-up tests or examinations) in the study?
Note: If the study involves research participant's visit, please describe the frequency. For studies with multiple visits, please attach the study schedule.

Each participants, both patient and caregiver, will be directly involved in study activities for 6 months. At baseline, only caregiver participants will be introduced to the digital tools, with standard care for the control arm being the AIC website and intervention being Careverse website. Over the course of the study, each participant will be administered four survey questionnaires according to the following schedule:

• Week 0 (start of the study):
  - Introduction to the study and Consent
  - Complete baseline questionnaire.
  - Introduction and registration to the digital tool (caregiver participants only). Control group will be directed to AIC website, whereas Intervention to Careverse website.

• Week 2 (7 days after the study begins):
  - Complete a questionnaire (first follow-up questionnaire)

• Week 7 (6 weeks after the study begins):
  - Complete a questionnaire (second follow-up questionnaire)

• Week 25 (6 months after the study begins):
  - Complete a questionnaire (third and final follow-up questionnaire)

G9. Attachment

G10. Please select the option(s) for re-identification in the case of incidental findings. More than 1 option can be selected if there are different plans for re-identification for different population of research participants.

☐ Yes, there are plans to re-identify and notify research participants.
☐ No, there is no plan to re-identify and notify research participants.
☑ There will not be any incidental findings arising from this study.

G10. (c) Please elaborate why there will not be any incidental findings arising from this study.

All data is collected via surveys with participants. No diagnostic tests are conducted and thus there will not be any incidental findings.

G11. Please provide details on sample size and power calculation. If applicable, please provide the means by which data will be analysed and interpreted.

Based on our prior results from a pre-post single arm feasibility study, the anticipated effects of the digital intervention on ACP engagement surrogate decision-making scale is 0.70. However, we assumed a conservative and smaller effect size of 0.50. We assumed a 6-point increase with a standard deviation of 12 points in ACP-SDM-17 score that would generate an effect size of this magnitude or greater. At 80% power (type II error rate at 20%), 5% significance level for a two-tailed test (type I error rate at 5%), three repeated measures of the primary outcome (one pre- randomisation and two post-randomisation) and an autocorrelation of 0.2, the design effect modification is 0.64 and the required total sample size is 80 caregiver participants in total (40 per allocation arm). We further assume a drop-out rate of 20%, thus increasing the target sample size to 100 caregiver participants in total (50 per arm). As a result, the study aims to recruit 100 caregiver and their 100 care recipients, totalling 200 participants.

Data will first be summarized using summary statistics such as mean (SD) and median (minimum, maximum) values for continuous variables, and frequency (proportions) for categorical variables, by randomization group as well as by site of
recruitment. Two sample t-test and Mann-Whitney test will be used to compare the profile of continuous variables between respective outcome groups. Associations between categorical variables and outcomes will be evaluated using Fisher's exact test or Chi-square test where appropriate.

We will use a generalized linear mixed model with the appropriate link function and distribution to compare the two arms with respect to the primary and secondary outcomes using an intention-to-treat approach. We will run models with and without controlling for differences in baselines values, health status and age. Mixed-effects models allow for inclusion of data from participants with missing data. Disease condition will be included as a random effect to evaluate and accommodate clustering effects. We will examine within-individual covariance to determine the appropriate variance–covariance structure to be used in the model. As robustness checks, we will also perform the above analyses using per-protocol approach by classifying participants into intervention or control group based on their actual exposure to and usage of the digital tools. All analyses will be performed using STATA/R and results will be assessed on a 5% significance level with 95% confidence intervals.

G11. (a) If this is part of an international study, please also state the approximate total number of worldwide research participants targeted for enrolment into this study. *
Number of worldwide research participants

G12. Please state the target number of research participants to be enrolled for each study site. If the exact numbers are not available, please give an approximate number range for Enrolment Target.
Note:

(1) For the distribution of Males, Females and Children to be enrolled into the study, please use the Enrolment Target Minimum number to provide an approximate distribution ratio.

(2) Please note that enrolling research participants beyond the Enrolment Target Maximum without the IRB's approval would constitute a non-compliance. If you intend to recruit beyond the Enrolment Target Maximum, please submit a study amendment to increase the enrolment target for approval.

(3) Enrolment Target Min must be equal or lower (≤) than sum of male, female, and children. Enrolment Target Max must be more than or equal (≥) to Enrolment Target Min.

Study Site	Enrolment Target Min	Enrolment Target Max	Adults (Male)	Adults (Female)	Children
National University Hospital	200	240	100	100	0
NUS - Saw Swee Hock School of Public Health	0	0	0	0	0

G13. Please list the inclusion criteria. The age group of the research participants must be specified. If you have more than 1 research participant group, please list the inclusion criteria for each group (if applicable).

For patients:

(1) Singapore resident aged 21years and above.

(2) Illness criteria:

a. Group 1: Patients with brain tumours: histological and/or radiological diagnosis of glioma or brain metastases. This patient group will be recruited from Department of Neurosurgery at NUH.

b. Group 2: Patients with spontaneous intracerebral haemorrhage (SICH) based on radiological diagnosis of SICH on baseline computed-tomographic scans. This patient group will be recruited from Department of Neurosurgery at NUH.

c. Group 3: Patients with CKD Stage 4 and 5, identified at G4 or G5 of CKD, glomerular filtration rate (GFR) 30 ml/min or less. This patient group will be recruited from Department of Medicine at NUH.

(3) patient or physician able to identify one main caregiver in the care and medical decision-making for the patient;

(4) ACP assessed to be appropriate for the patient by physicians.

(5) Able to communicate in either English, Chinese, Malay, or Tamil.

For caregivers:

(1) Adults identified as NOK for patients that meet the criteria above

(2) Singapore resident aged 21years and above

(3) Able to communicate in English

G14. Please list the exclusion criteria. If pregnant women will be excluded from the study, please state clearly. If you have more than 1 research participant group, please list the exclusion criteria for each group (if applicable).

The exclusion criteria are:

For patients:

(1) Unable to identify a caregiver who is a decision-maker

(2) Patients are current and previous healthcare worker

(3) Patients have participated in any of our caregiving website study.
(4) Patients diagnosed with dementia (from medical record) or Cognitively impaired (i.e. fail cognitive check Abbreviated Mental Test (AMT))
The cut-off points for AMT:
0 to 6 years of education: 74 Years Old and younger: 8 or more correct; 75+ years Old: 6 or more correct
More than 6 years of education: 74 Years Old and younger: 9 or more correct; ; 75+ years Old: 9 or more correct

For caregivers:
(1) Caregivers are current and previous healthcare worker
(2) Not involved in primary care of the patient (Including providing care to the patient (eg. accompanying patient for doctor's visits, helping the patient with day-to-day activities), supervision of care or involved in making decisions regarding treatment the patient receives)
(3) Diagnosed with dementia

G15. Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims.
As end-of-life (EoL) topics are highly sensitive and caregivers' attitudes, preferences, and readiness towards EoL care and arrangement may change over time, one limitation is that the proposed procedures do not allow us to assess the long-term effect of our digital intervention on the outcomes of interest. This limitation can be addressed in the future by conducting a longitudinal cohort study to assess the effect of using such digital tool patients and caregivers' decision and outcomes in long run. Another limitation of this design is that we may not be sufficiently powered to measure the impacts on "conditional outcomes", ie. things are that very specific to decisions and dependent on other events happening, ie. patients passing away to measure bereavement outcomes. This limitation could be addressed in the future by conducting a followup study, specifically focusing on bereaved caregivers to compare the longer term effects of the intervention on bereavement outcomes.

G16. What are the potential risks to research participants?
☐ Economic risk
☐ Physical risk
☑ Psychological risk
☐ Social risk
☐ Legal risk
Due to the sensitive nature of the topic, there is a risk of distress and sensitivity to both patients and caregivers. This may occur when patients and caregivers are going through the digital intervention and/or answering the survey questions.
To mitigate this potential risk, the PI will affirm that it is normal to experience raw emotions when talking about our loved ones who are ill at the start of the interview. During the interview, the PI will continue to check in with the participant to ensure that he/she is still comfortable to continue with the interview, or needs a break to collect his/her emotions, wishes to skip answering certain questions (which is acceptable by the study team), or wishes to stop the interview. If the participant manages to complete the interview, the PI will let him/her know how helpful he/she has been and reiterate that it is alright to experience raw feelings about a loved one who is seriously ill or has passed on. Participants may choose to not continue with the questionnaire and withdraw

from the study at any point in time and their data will be discarded. Support systems such as family or religion may be suggested by the PI for the participant's consideration. In case of the emergence of suicide ideation, the PI will provide hotlines to the participant such as the SOS hotline (1800-221-4444) or the National Care hotline (1800-202-6868). The PI will also share that it is advisable for the participants to seek assistance from their own counsellors or professional therapists.

G17. What are the potential benefits (direct as well as indirect) to research participants? Indirect benefits may refer to the medical knowledge gained in the future, from the research.

There is no known direct benefit from participation. However, the potential benefit of this study is that this may ultimately lead to the development and implementation of an interactive web-based digital program that is specially crafted to suit the needs of caregivers of patients with serious illness and their care recipient, which in turns may enable caregivers and patients to make a treatment decision that aligns with their personal values, improving the treatment decision making process and improve health outcomes of caregivers.

G18. What is the estimated duration required to conduct this study?

Estimated Duration: 2 Years and 0 Months

G19. Does this study have a study protocol?

◯ Yes

◉ No

Section J: Recruitment Details and Consent Process

J1. How will potential research participants be identified? Please tick all the applicable boxes.

☑ Referral by attending healthcare professional

☑ Research participants with dependent relationship related to the study team (e.g. doctor-patient, employee-employer, head subordinate, student-teacher)

☐ Databases

☐ Other methods of research participant identification

J1. (a) Please describe how the study team will manage the dependent relationship to prevent coercion or undue influence.

Patient participants will be recruited from clinics of study team members. To mitigate the risk of influence on patient physician relationship, the physicians in the study team who are involved in providing direct care to the patient will not be involved in consent taking. Consent will be administered by the research coordinators instead. Should the potential research participants, both patients and next-of-kin (NOK) caregivers, choose not to participate in the study, their wish will be respected, and they will continue to receive standard, routine care and management. In no way will the care and management of the participants be different from the standard, routine care and management should they choose to participate in the study or not.

J2. Please describe the advertising/ recruitment strategies (e.g., talks in public place, societies etc.) and if any, attach the recruitment materials (e.g., poster/brochure/advertisement in newspaper/radio, etc.) to be used to recruit research participants.

Not applicable. Participants will be identified based on eligibility and approached for recruitment by study team members.

J2. Attachment

J3. Are there any recruitment restrictions based on the gender of the research participants (e.g. only males will be included in this study) or race of the research participants (e.g. only Chinese research participants will be included in this study)?

○ Yes
◉ No

J4. Who will make the first contact with research participants and how will the research participants be contacted?

First contact with participants will be made by the clinic staff (clinic case managers, care coordinators) and the study team (site-PI); Patients will be asked if they are keen to participate in a research study before the study team members approach for study introduction and recruitment. Measures will be put in place in situations where participants have a direct relationship with the study team to mitigate the risks of undue influence or coercion for the participants to join this study, such as sufficient time will be provided to the participants for them to consider their participation and voluntary participation will be emphasized.
No advertising/publicity material will be used.

J5. Please select the mode of obtaining consent:

☑ Consent will be obtained in-person (face-to-face consent)
☑ Consent will be obtained remotely (remote consent)

J5. (a) Please explain why consent must be obtained remotely.

Remote consent will only be available to caregiver participants. The study aims to recruit next-of-kin caregivers of patients with serious illness. Remote consent will be allowed for use when potential NOK caregivers are unable to accompany eligible patients for clinic visits and thus unable to give face-to-face consent. This is to allow for more efficient and effective recruitment effort.
For patient participants, informed consent will only be obtained face-to-face.

J5. (b) Please elaborate when face to face consent and remote consent would be used.

For eligible patient participants, only face-to-face consent will be taken and will be taken during patient's hospital visits.
For eligible caregiver participants, face-to-face consent will be used when NOK caregivers are present at the study site during patient's visits. If NOK caregivers are unable or unavailable to be present at the patient's clinic, remote consent would be collected via online meeting channel (Zoom).

J6. Describe the face-to-face consent process.

For potential patient participants, face-to-face consent will take take in the waiting room at the outpatient clinic before or after patient's appointment (for advanced kidney disease patients) or in the ward (for inpatient symptomatic intracerebral hemorrhage stroke or brain tumor patients) during visiting hours.
For potential NOK caregiver participants, face-to-face consent will take take in the waiting room at the outpatient clinic before, during, or after patient's appointment (for advanced kidney disease patients) or in the ward (for inpatient symptomatic intracerebral hemorrhage stroke or brain tumor patients) during visiting hours.
Before approaching potential participants for consent-taking, research coordinators will ensure that patient's privacy is maintained throughout the session.

J7. Describe the remote consent process.

The study team first contacts the participant and arranges for a virtual/tele-consult session to obtain the informed consent, in the presence of a prescribed witness. The virtual/tele-consult will be done using Microsoft Teams or Zoom, both are NUS and NUH-approved platform for consent-taking, via the secured account of study team members. The study team will remind the participant that the signed consent process will have to take place in a private room or their home, that is free of distraction and intrusion. All parties (study team, witness and participant) will have to keep their web camera on to ensure that he/she stays throughout the session. Screensharing would be used but the meeting will not be recorded.
The workflow is as follow:
1) Study team members verify of identity e.g NRIC, and/or date of birth, which may be either physical or through their Singpass applications. No records will be kept.
2) Study team members share screen function to go through the informed consent form.
3) Participants will be sent a PDF or word document form and will sign the form.
4) The form will be sent back to the study team for the investigator to sign the same form in the presence of the participant.
5) The participant will then be provided with an electronic copy of the signed form via an institution email address.
6) The subject is required to acknowledge the receipt of email.

All participants will be given adequate time to decide on whether they wish to participate, with efforts taken to ensure that there will be no coercion or undue influence towards the participants. Refusal to participate in the study will be respected and addressed professionally. The consent form will be attached in a separate document, and will delineate the objectives, procedures, benefits and risks of enrolling into the study.

J8. Who will take consent from potential research participants/legally acceptable representatives (e.g., PI, Co-Investigators etc.)?

Trained research coordinators team members.

J10. Will research participants receive any monetary payments (e.g. transportation allowances) or gifts for their participation in the study?

◉ Yes

○ No

J10. (a) Please elaborate.

For caregiver participants, the study incentive schedule is as follows: CG participants will be reimbursed SGD30 upon completion of the baseline survey and successful signup to the allocated treatment (T0); SGD25 each upon the completion of the first (T1) and second (T2) follow-up survey; and SGD20 upon the completion of the final survey (i.e. SGD 100 in total).
For patient participants, the study incentive schedule is as follows: patient participants will be reimbursed SGD30 upon completion of the baseline survey; SGD20 each upon the completion of the first (T1) and second (T2) follow-up survey; and SGD15 upon the completion of the final survey (i.e. SGD 85 in total).
All reimbursement will be done via cash or cashless payment based on participants' preference.

J11. Will the study enroll non-English speaking research participants?

◉ Yes
○ No

J11. (a) What are the possible languages that will be understood by the prospective research participant or the legal representative

☑ Chinese
☑ Malay
☑ Tamil
☐ Others

J11. (b) How will the non-English consent be documented?

☐ Informed Consent Form (Full) translated to the language understood by the prospective research participant or legal representative.
Note: Submission of translated consent form and certificate of translation is not required. These documents should be filed in the investigator/study file.
☑ Informed Consent Form (English) with DSRB Short Consent Form Template (Translated).
☐ Informed Consent Form (English) with other Short Consent Form (Translated).
☐ Verbally translated using Informed Consent Form (English) in the presence of impartial witness.

J12. Do you have any additional comments regarding the Informed Consent process?

○ Yes
◉ No

J13. Please attach the Informed Consent Document(s).

PISCF_Careverse_Caregiver (EN)_2025-06-30 (V2)_clean.docx [14 Jul 25 11:58:53]
PISCF_Careverse_Caregiver (EN)_2025-06-30 (V2)_tracked.docx [14 Jul 25 11:58:53]
PISCF_Careverse_Patient (EN)_2025-07-21 (V2.2)_clean.docx [21 Jul 25 09:56:42]
PISCF_Careverse_Patient (EN)_2025-07-21 (V2.2)_tracked.docx [21 Jul 25 09:56:42]

Section T: Research Data Confidentiality

T1. Please select the mode of identification for the research data at the point of collection of research data.

○ Research data are coded and the code is maintained by third party
◉ Research data are coded and the code is maintained by study team
○ Identifiers present
○ Other methods

T2. Please state how the research data will be protected to ensure confidentiality and security.
☑ Hardcopy data will be stored in designated locked location (e.g. cabinet(s), room(s), etc) that are accessible to authorized study personnel only
☑ Electronic data will be stored in institution approved secure, and encrypted storage medium, such as databases, encrypted portable media (e.g. USB drives, CD/DVD, hard disks), and/or institution approved online storage platforms. The electronic data will not contain research participant identifiers. Identification code linking electronic data and research participants will be stored separately.

T3. Describe who will have access to the research data, and how the access will be controlled and monitored?
Only research team members and collaborators listed in this DSRB application will have access to the research data. Access to the study data will be monitored and recorded by the Study Lead.

T4. How will the research data be managed upon study completion?
◉ The research data will be destroyed after it has been stored for the minimum duration of retention as specified by the institutional policy
○ The research data will be used for future research

Section V: Research Data - Use of software or mobile applications

V1. Please select the type of software(s) applicable and the name of software (including third party and mobile applications) Please also attach the supporting documents (if any):
☐ V1. (a) Telehealth Medical Device
☐ V1. (b) Telehealth Wellness Device
☑ V1. (c) Others

V1. (c) Others
We have customised software on the website to present tools and save inputs for caregivers to review. Selected webpage screenshots are attached below.

V1. (c) Attachment
Intervention_Careverse app.pdf [30 May 25 12:23:12]

V2. Please describe the following:
- **What data would be collected via the telehealth device?**
- **Where the data would be stored?**
- **Who have access to the data?**
- **How would the research data confidentiality be protected?**

In our servers, we collect and store usernames, emails, site usage data, tools data inputs that are linked to username and participant ID. No identifiable information, including NRIC/FIN numbers, names, birthdays, or ethnicities, will be collected.
Only research team members and those listed and approved in the study DSRB are allowed access to these data.
Data privacy and security managed through Amazon Web Services (AWS) services and all data are stored in AWS Data centers located in Singapore. We use AWS because it employs a robust set of security and privacy measures aligned with local regulations, including the Personal Data Protection Act (PDPA) and Health Insurance Portability and Accountability Act (HIPAA). We store the study data in the Singapore regional server to meet data residency and sovereignty requirements, with encryption using KMS services. Additional, we use tools like AWS IAM (for Identity Access Management) and CloudTrail (to monitor, log, and retain account activity of research team). This setup supports privacy, access control, and auditability, and enables us to ensure the system is secure and compliant.

V3. Assurances by Principal Investigator.

- **The use of usage of the software or a mobile application and storage of data will be in compliance with institution policy.**

☑ I agree with the above statement.

Other Attachments

Note: Additional documents may be attached here. Documents relevant to the respective sections should not be attached here.

MOA for NUS-NUHS - Amendment (Gerald Koh)22_230601(EXE)_Fully Exe.pdf [30 May 25 18:38:32]

Declaration of Principal Investigator/ Site-Principal Investigator

This is the Principal Investigator's Declaration.

- I will not initiate this study until I receive approval notification from IRB and regulatory authority approval (if applicable).
- I will not initiate any change in the protocol without prior written approval from IRB, except when it is necessary to reduce or eliminate any immediate risks to the research participant. Thereafter, I will submit the proposed amendment to the IRB and other relevant authority for approval.
- I will promptly report any unexpected or serious adverse events, unanticipated problems or incidents that occur in the course of this study.
- I will maintain all relevant documents and recognize that the IRB staff and regulatory authorities may inspect these records.
- I understand that failure to comply with all applicable regulations, institutional and IRB policies and requirements may result in the suspension or termination of this study.
- I declare that there are no existing or potential conflicts of interest for any of the study team members participating in this research study and their immediate family members. If there are, I have declared them in the relevant section of this application form or NHG Conflict of Interest Declaration Form.

I confirm that I have read, understood and accept the Principal Investigator's Declaration above.
(Note: PI declaration is required only for new applications or applications requesting significant amendments.)

Site	Principal Investigator	Study Role	Email	Declaration	Date
NUS - Saw Swee Hock School of Public Health	Prof Koh Gerald	PI	ephkohch@nus.edu.sg	Completed	14-Apr-2025

Endorsements Page

Department Representative Endorsement

The Department Representative can be the Head/ Chief/ Research Head of the PI's Department. Should the Head or Chief be the PI or Site-PI, then their reporting officer should complete this Section. It is assumed that all Departments involved concur with the PI's Department Representative.

1. Significance: The study addresses an important problem and affect concepts and methods that drive the field.
2. Approach: The conceptual framework is adequately developed. The design, methods, and analyses are adequately developed and appropriated.
3. Innovation: The study challenges existing paradigms. The study employs novel concepts, approaches and methods.
4. Principal Investigator: The Principal Investigator are appropriately trained to conduct this study and have evidence of commitment (e.g., previous track record).
5. Environment: The study site(s) are suited to conduct the study. There are adequate patient pool and adequate resources.
6. Budget: The proposed funding or budget are reasonable and sufficient for the study.
7. Time: The Principal Investigator has adequate resources and time to conduct and complete the study.

Name	Department	Institution	Date
A/Prof Falk Mueller-Riemenschneider	NUS - Saw Swee Hock School of Public Health	NUS - Saw Swee Hock School of Public Health	06-May-2025
Dr Kok Hong Dedrick Chan	Surgery	National University Hospital	14-Jun-2025

Institution Representative Endorsement

The Institution Representative has been determined by your institution as the authority that declares whether your research is in keeping with the institution's research objectives, reputation and standards.
I acknowledge that this research is in keeping with standards set by my Institution.

Name	Institution	Date
A/Prof Falk Mueller-Riemenschneider	NUS - Saw Swee Hock School of Public Health	06-May-2025
A/Prof Tham Elizabeth	National University Hospital	16-Jun-2025