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## **CURATE.AI COR-Tx platform as a digital therapy and digital diagnostic for cognitive function in brain tumour patients post-radiotherapy treatment: Protocol for a prospective mixed-methods feasibility clinical trial**

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Manuscripts

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3 **CURATE.AI COR-Tx platform as a digital therapy and digital diagnostic for**  
4 **cognitive function in brain tumour patients post-radiotherapy treatment:**  
5 **Protocol for a prospective mixed-methods feasibility clinical trial**  
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## 1 **ABSTRACT**

### 2 **Introduction**

3 Conventional interventional modalities for preserving or improving cognitive function  
4 in brain tumour patients undergoing radiotherapy usually involve pharmacological  
5 and/or cognitive rehabilitation therapy administered at fixed doses or intensities, often  
6 resulting in sub-optimal or no response, due to the dynamically evolving patient state  
7 over the course of disease. The personalisation of interventions may result in more  
8 effective results for this population. We have developed the CURATE.AI COR-Tx  
9 platform, which combines a previously validated, artificial intelligence-derived  
10 personalised dosing technology with digital cognitive training.

### 12 **Methods and analysis**

13 This is a prospective, single-centre, single-arm, mixed-methods feasibility clinical trial  
14 with the primary objective of testing the feasibility of the CURATE.AI COR-Tx platform  
15 intervention as both a digital intervention and digital diagnostic for cognitive function.  
16 Fifteen patient participants diagnosed with a brain tumour requiring radiotherapy will  
17 be recruited. Participants will undergo a remote, home-based 10-week personalised  
18 digital intervention using the CURATE.AI COR-Tx platform three times a week.  
19 Cognitive function will be assessed via a combined non-digital cognitive evaluation  
20 and a digital diagnostic session at five time points: pre-radiotherapy, pre- and post-  
21 intervention and 16- and 32-weeks post-intervention. Feasibility outcomes relating to  
22 acceptability, demand, implementation, practicality and limited efficacy testing as well  
23 as usability and user experience will be assessed at the end of the intervention through  
24 semi-structured patient interviews and a study team focus group discussion at study  
25 completion. All outcomes will be analysed quantitatively and qualitatively.

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6 **27 Ethics and Dissemination**7  
8 28 This study has been approved by the National Healthcare Group (NHG) DSRB  
9  
10 29 (DSRB2020/00249). We will report our findings at scientific conferences and/or in  
11  
12 30 peer-reviewed journals.  
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17 **32 Trial registration**18  
19 33 NCT04848935  
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22 3423  
24 **35 Keywords**25  
26 36 Digital therapeutics, artificial intelligence, brain tumour, radiotherapy, feasibility,  
27  
28 37 personalised medicine, cognitive rehabilitation, clinical trial  
29  
30  
31 3832  
33 **39 Word Count**34  
35 40 4300  
36  
37  
38 4139  
40 **42 Strengths and limitations of this study**

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- 42 43 • This is a prospective, mixed-methods feasibility trial to inform a future clinical
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- 44 44 trial.
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- 46 47 • The behavioural component will provide insights into how to further develop
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- 48 48 the intervention for the patient population as well as how to scale for a larger
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- 50 49 the intervention for the patient population as well as how to scale for a larger
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- 52 50 multisite randomised control by including patients and study team members
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- 54 51 (clinicians/data team members).
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3 49 • This feasibility trial is a model for a decentralised trial in which patients can  
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5 50 undergo treatment in the comforts of their own home and clinicians can  
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7 51 monitor their progress.  
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10 52 • The non-randomised single-arm feasibility trial does not simulate a  
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12 53 randomised control trial as closely as a randomised pilot and is limited in  
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14 54 informing on issues that may arise from the logistical process on a larger  
15  
16 55 scale.  
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19 56 • The digital nature of this intervention requires a higher level of technological  
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21 57 literacy and skills which may be intimidating to some, introducing potential  
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23 58 bias in recruitment and may have limited generalisability to other countries  
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26 59 owing to cultural differences.  
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## 60 INTRODUCTION

61 Patients with brain tumours who undergo radiotherapy exhibit cognitive impairments  
62 throughout the course of their condition. These impairments often include decline in  
63 memory, attention and executive function, and they can be attributed to the tumour  
64 itself and/or side effects of its treatment [1–5]. Cognitive deficits are reported to occur  
65 before radiotherapy treatment and in between 50-90% of adult patients six months  
66 after treatment [1,6–8]. Such high prevalence, coupled with the increase in life  
67 expectancy of brain tumour patients necessitates the need for appropriate strategies  
68 that preserve and improve cognitive functioning in brain tumour survivors.

69  
70 To date, pharmacological interventions and cognitive rehabilitation therapy (CRT)  
71 have been the main approaches used to preserve and improve cognitive functioning  
72 in these patients [1]. Pharmacological interventions typically include repurposed  
73 medications for cognitive functioning in other conditions, such as donepezil,  
74 armodafinil, modafinil and methylphenidate [1]. However, evidence of the efficacy of  
75 these pharmacological interventions is limited and trial endpoints are often unmet [1,9–  
76 12]. CRT involves neuropsychological interventions that are meant to augment various  
77 domains of cognitive function through the mechanism of neuroplasticity [1]. CRTs can  
78 be provided directly to an individual or in group settings, conducted at home or in  
79 dedicated rehabilitation centres, and delivered face-to-face by a qualified clinician as  
80 pen-and-paper exercises or through computerised programmes [1]. CRTs have shown  
81 promise with improvements in desired cognitive performance reported after their use  
82 in some patients [1,9,13]. However, these findings are limited and inconsistently  
83 reported across studies, warranting further development of more robust CRTs for this  
84 population.



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3 85 In both the pharmacological and CRT modalities, the reported treatment regimens are  
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5 86 typically administered as a one-size-fits-all intervention with fixed doses or training  
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7 87 intensities for the duration of the treatment for all patients. However, not only does the  
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9 88 state of patient typically evolve over the duration of their condition, but each patient  
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11 89 also experiences variable factors, such as tumour burden (e.g., size, position, and  
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13 90 type), baseline cognitive abilities, treatment type and response (e.g., efficacy, side  
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15 91 effects, etc.). As such, it remains possible that these uniform one-size-fits-all, fixed  
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17 92 dose interventions are a large contributing factor to the sub-optimal responses  
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19 93 experienced by some patients [14]. To be more effective, interventions that aim to  
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21 94 preserve and improve cognitive functioning should treat each patient as an individual  
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23 95 case, with the treatment tailored to that individual. Therefore, there is an urgent need  
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25 96 to develop therapies that are personalised and that can dynamically adapt throughout  
26  
27 97 the course of the condition for brain tumour patients that undergo radiotherapy.  
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29 98 Recently, artificial intelligence (AI) has established itself as a paradigm-shifting  
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31 99 technology in healthcare with the potential to transform many aspects of patient care,  
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33 100 if used appropriately [15]. In particular, AI shows great potential in personalising care  
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35 101 for patients from diagnosis to treatment selection and optimising intervention [14,16].  
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37 102 As such, integrating AI into CRTs is a plausible solution to overcome the  
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39 103 aforementioned challenges and pitfalls of the current one-size-fits-all, fixed dose  
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41 104 interventions.  
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51 106 Commonly, AI health technologies are developed from the big data paradigm in which  
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53 107 population data and advanced statistical analyses are harnessed to diagnose and treat  
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55 108 individual patients based on their demographics and disease history [17]. These are  
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57 109 often highly successful, but require large population datasets and substantial prior  
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3 110 knowledge of the targeted condition in order to personalise care and avoid common  
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5 111 biases [14,16,18]. Further, while these methods can account for inter-patient variability  
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7 112 to identify appropriate care strategies, they have limited ability to account for the intra-  
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9 113 patient variability of a dynamically changing patient state throughout the course of their  
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11 114 condition [14]. In contrast to the big data paradigm, small data paradigm AI health  
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13 115 technologies framed to serve N-of-1 medicine require as little as only a patient's own  
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15 116 data to deliver personalised care by rapidly capturing their own response to a  
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17 117 treatment over time [14,16,19,20]. AI for N-of-1 medicine may be a favourable  
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19 118 approach to dynamically modulate an intervention with the goal of optimising the  
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21 119 efficacy for a patient over time [19]; and therefore has potential to improve  
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23 120 interventions aimed at preserving and improving cognitive function in brain tumour  
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25 121 patients.  
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33 123 CURATE.AI is a small data, AI-derived, indication-agnostic and mechanism-  
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35 124 independent platform that maps the relationship between an intervention intensity  
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37 125 input and the phenotypic response output for a patient, using exclusively their own  
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39 126 data [21]. It is based on a previously established observation that a quadratic surface  
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41 127 can closely represent the relationship between varying intervention intensities input  
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43 128 and measurable phenotypic response output in a human system [22–27]. Using this  
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45 129 premise, the platform is prospectively calibrated by correlating patient-specific  
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47 130 responses to a range of intervention intensities to create a patient's individualised  
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49 131 CURATE.AI profile. The prospectively calibrated profile is then paired with an intensity  
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51 132 optimisation process to predict the patient's phenotypic response output for a specified  
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53 133 intensity input and to provide treatment intensity recommendations for optimised  
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3 134 results. Importantly, the individualised CURATE.AI profile can be continuously  
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5 135 recalibrated as the patient evolves throughout the course of their condition.  
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10 137 To date, the validity of CURATE.AI has been successfully demonstrated, both  
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12 138 retrospectively and prospectively, for single drug optimisation of immunosuppression  
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14 139 therapy [28] and for combination drug optimisation of oncology therapy [29,30]. Most  
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16 140 recently, CURATE.AI was demonstrated as an integral part of a cognitive training  
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18 141 platform to derive individualised learning profiles for young adults [31]. More  
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20 142 specifically, in the prospective, proof-of-concept study, the CURATE.AI platform was  
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22 143 used to derive personalised learning profiles of healthy participants while they  
23  
24 144 completed a multitasking cognitive training paradigm. The personalised learning  
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26 145 profiles were generated by correlating a participant's performance improvement to  
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28 146 their performance at various intensities of the multitasking cognitive training paradigm.  
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31 147 Overall, these profiles revealed substantial differences between individual  
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33 148 performance at various intensity levels and demonstrated that individual-specific  
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35 149 exposure to different training intensities is required to achieve maximum performance  
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37 150 improvement during the multitasking cognitive training paradigm. The ability of the  
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39 151 CURATE.AI platform to identify individualised training profiles provides the foundation  
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41 152 for the optimisation of non-pharmaceutical therapies, such as CRTs.  
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49 154 Therefore, to address the urgent clinical need for a dynamic, personalised therapy that  
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51 155 is effective in preserving and improving cognitive functioning in brain tumour patients  
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53 156 who undergo radiotherapy, we have developed the CURATE.AI COR-Tx platform as  
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55 157 a digital therapeutic (DTx) with the potential to be used as a treatment and diagnostic  
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57 158 tool. DTx are evidence-based software programmes that prevent, manage or treat a  
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3 159 medical condition or disease that can be used independently or together with other  
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5 160 modalities to deliver care directly to patients [32]. DTx are typically easily deployable  
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8 161 for at-home use and efficacy measurements (e.g., scoring) can be given back to the  
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10 162 individual as feedback. both of which may contribute to improved patient compliance  
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12 163 and efficacy [16]. The CURATE.AI COR-Tx platform combines CURATE.AI with tablet-  
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14 164 ready digital cognitive training tasks as the interface. The CURATE.AI COR-Tx  
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16 165 platform can dynamically optimise the treatment for the entire duration a patient's care.  
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18 166 This may result in improved cognitive function in these patients, as compared to  
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20 167 traditional one-size-fits all, fixed-intensity CRTs, and potentially serve as an effective,  
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22 168 interventional modality for brain tumour patients that undergo radiotherapy. Further,  
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24 169 as the CURATE.AI COR-Tx platform can be used throughout the duration of the  
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26 170 condition, from initial diagnosis to after radiotherapy treatment, it is possible that  
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28 171 performance measures captured by the digital cognitive training tasks may have the  
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30 172 capacity to remotely establish cognitive function levels by detecting and monitoring a  
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32 173 patient's own ability and changes at dedicated time points and over time.  
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## 175 **Objectives**

176 The primary objective of this trial is to test the feasibility of the CURATE.AI COR-Tx  
177 platform as a digital intervention (DI) and a digital diagnostic (DD) for cognitive function  
178 in post-radiotherapy brain tumour patients. The secondary objective of this trial is to  
179 assess the usability of the CURATE.AI COR-Tx platform. Further exploratory  
180 objectives are to assess user experience (UX) with the CURATE.AI COR-Tx platform.  
181 Additionally, as the participants will use the CURATE.AI COR-Tx platform throughout  
182 the duration of their care, it is possible that the objective, quantifiable physiological  
183 and behavioural data collected from the DTx, known as digital biomarkers, may offer

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3 184 the ability to detect changes in cognitive function, such as improvement or decline, in  
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5 185 these participants [33]. Therefore, an additional exploratory outcome will include  
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7 186 capturing and preliminary evaluation of potential digital biomarkers for cognitive  
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9 187 function during the DI sessions. The results of this clinical feasibility trial will provide  
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11 188 data required to design a definitive future multi-site randomised control trial (RCT) to  
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13 189 assess the efficacy of the CURATE.AI COR-Tx platform.  
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## 191 **METHODS AND ANALYSIS**

192 This trial is registered and published at ClinicalTrials.gov (NCT04848935). This  
193 protocol was prepared in adherence to the Consolidated Standards of Reporting  
194 Trials (CONSORT) extension for randomised pilot and feasibility trials reporting  
195 guidelines [34] and Standard Protocol Items: Recommendations for Interventional  
196 Trials (SPIRIT) [35].  
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197

### 198 **Trial design**

199 This is a prospective, single-centre, single-arm, mixed-methods feasibility clinical trial.  
200 The start date for this study was in April 2021 and is expected to run until April 2024.  
201 The outcome of this trial will provide data required to design a definitive, future, multi-  
202 site RCT. Criteria for progression to a future larger trial will be based on the combined  
203 qualitative and quantitative feasibility of primary and secondary outcomes.  
204

204

### 205 **Study setting and participants**

206 Fifteen patient participants will be recruited from the Department of Radiation  
207 Oncology, National University Cancer Institute Singapore (NCIS), part of the National  
208 University Health System (NUHS) in Singapore. Clinical investigators will recruit

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3 209 patients according to eligibility requirements during routine clinical visits prior to the  
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5 210 planned commencement of partial or whole brain radiotherapy. Written informed  
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7 211 consent will be gained from each participant prior to inclusion in this study. The rolling  
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9 212 recruitment period for this study is between May 2021 and July 2023. Participants that  
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11 213 are removed or drop out will not be replaced.  
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### 16 17 215 **Eligibility criteria**

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19 216 Inclusion criteria: Patient participants (1) with a neoplastic condition (benign or  
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21 217 malignant) involving the brain or skull requiring radiotherapy (with or without  
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23 218 chemotherapy); (2) aged  $\geq 21$  years; (3) Eastern Cooperative Oncology Group  
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25 219 (ECOG) Performance Status of 0 to 2; and (4) with a life expectancy of at least six  
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27 220 months.  
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33 222 Exclusion criteria: Patient participants (1) undergoing stereotactic radiosurgery (single  
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35 223 fraction); (2) undergoing re-irradiation to the same area of the brain; (3) unable to give  
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37 224 informed consent; (4) who cannot understand spoken English language; (5) physically  
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39 225 incapable of using a computer tablet (either due to vision loss or dominant hand  
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41 226 weakness); and (6) who are pregnant or breastfeeding women.  
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### 46 47 228 **Consent Procedure**

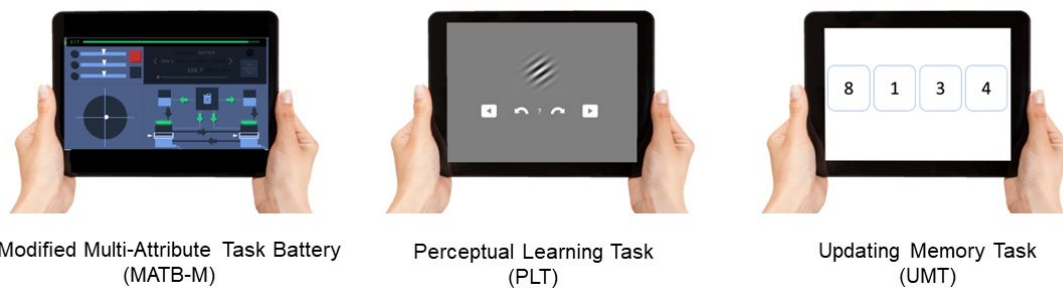
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49 229 The lead clinical coordinator will meet potential participants at their outpatient  
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51 230 appointment where they will be provided with a consent form, participant information  
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53 231 leaflet and a verbal explanation of the study. Participants who are willing to take part  
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55 232 in the study will sign a consent form and an appointment for baseline testing prior to  
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57 233 commencement of their radiotherapy treatment will be scheduled.  
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235 **Intervention**236 **CURATE.AI COR-Tx Platform**

237 The CURATE.AI COR-Tx platform involves in-house developed tablet adaptations of  
 238 multitasking, perceptual learning and executive processing digital cognitive training  
 239 tasks which serve as the interface of the DI and DD. In the DI, the intensity of each  
 240 task will be independently modulated by CURATE.AI, described in detail in  
 241 subsequent sections, resulting in a dynamically personalised DTx CRT for each user.  
 242 In the DD, the intensity of each task will be fixed and predefined for all users. One or  
 243 more of the digital cognitive training tasks may serve as the interface for the  
 244 CURATE.AI COR-Tx DI or DD. The digital cognitive training tasks of the CURATE.AI  
 245 COR-Tx platform are depicted in Figure 1 and described in detail below.

246



247

248 **Figure 1.** CURATE.AI COR-Tx platform digital cognitive training tasks

249

250 ***Modified Multi-Attribute Test Battery***

251 The Multi-Attribute Test Battery (MATB) is a flight deck simulator originally developed  
 252 by the National Aeronautics and Space Administration [36] and further redefined by  
 253 the United States Air Force [37]. MATB is a multitasking paradigm that requires users  
 254 to respond to the demands of four tasks simultaneously. The tasks require users to  
 255 respond to auditory commands, track a target with a joystick, monitor system gauges



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3 256 for deviant readings and problem-solve to maintain fuel levels. The software was  
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5 257 originally developed to be played on a computer with a monitor, joystick and  
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7 258 headphones. In this current trial, participants will use a modified version of MATB  
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10 259 (MATB-M) that our research team has developed. MATB-M is a tablet-ready,  
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12 260 modernised and gamified adaptation of MATB that allows for remote operation (Figure  
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14 261 1). MATB-M still replicates the functionality of MATB without the auditory command  
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16 262 task and requires a user to complete multiple subtasks simultaneously. The intensity,  
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18 263 or difficulty, of each subtask within MATB-M can be modulated, primarily by adjusting  
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20 264 the frequency of critical events that demand evaluation and/or response. Performance  
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22 265 is measured by a composite score of accuracies and reaction times in event solving  
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24 266 of the individual tasks.  
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### 31 268 Perceptual Learning Task

32  
33 269 The perceptual learning task (PLT) is an online adaption of the orientation  
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35 270 discrimination task with Gabor patches from Lengyel & Fiser (2019) (Figure 1) [38].  
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37 271 Users are first shown a reference Gabor patch followed by a modified test Gabor patch  
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39 272 that may be oriented clockwise or counter-clockwise. Users are required to indicate  
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41 273 the direction of rotation. Difficulty can be adjusted by changing the degree of similarity  
42  
43 274 between the two stimuli or by changing the stimuli's visual contrast levels.  
44  
45 275 Performance is measured by the accuracy of correct discriminations.  
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### 49 276 Updating Memory Task

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51 277 The updating memory task (UMT) is an online adaptation of the number memory task  
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53 278 protocol from Morris & Jones (1990) (Figure 1) [39]. In this task, a list of several  
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55 279 numbers or letters will be presented serially for a designated time per item. Users are  
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57 280 required to recall the last four items presented in the list. Difficulty can be adjusted by  
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3 281 increasing the length of the list of items presented. Performance is measured by the  
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5 282 accuracy of correctly recalled sequences.  
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9  
10 284 **CURATE.AI**

11  
12 285 CURATE.AI in this context refers to the CURATE.AI software used in the backend of  
13  
14 286 the CURATE.AI COR-Tx platform that generates the calibrated, individualised profiles  
15  
16 287 and subsequent training intensity recommendations for a DI training session. The  
17  
18 288 Health Sciences Authority in Singapore classifies CURATE.AI as a Class B medical  
19  
20 289 device (low to moderate risk), which is defined as all active therapeutic devices that  
21  
22 290 are software, or which are intended to administer or exchange energy to, or with the  
23  
24 291 human body. We have filed the accompanying Clinical Research Materials notification  
25  
26 292 (CRM-N) under the National University of Singapore, for the intended purpose of  
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28 293 providing training intensity recommendations within this clinical feasibility trial.  
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35 295 *CURATE.AI recommendation*

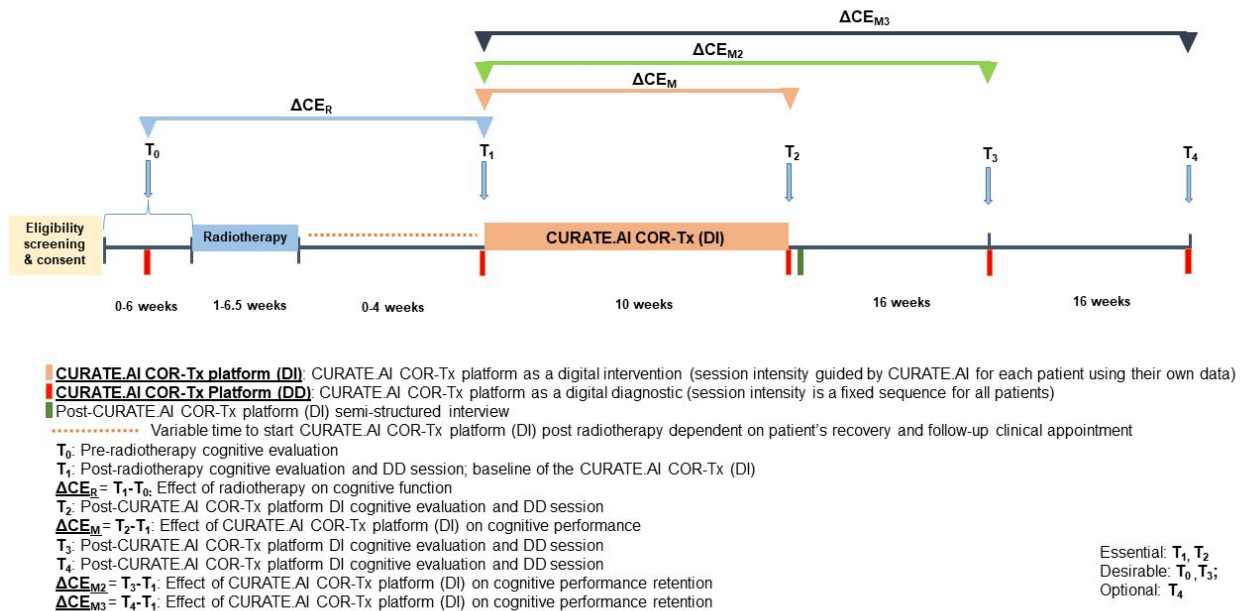
36  
37 296 CURATE.AI will be used to provide training intensity recommendations for the DI  
38  
39 297 component of the CURATE.AI COR-Tx platform. In CURATE.AI-guided training  
40  
41 298 sessions, for each participant, CURATE.AI will undergo an initial calibration period  
42  
43 299 with the aim of generating a personalised profile based on the treated participant's  
44  
45 300 own data only. During this initial calibration period, CURATE.AI will provide calibration-  
46  
47 301 intent training recommendations to collect data on the participant's phenotypic  
48  
49 302 response, as measured by their performance, to a range of training intensities on a  
50  
51 303 given DI task. CURATE.AI will then provide dynamic intensity recommendations for  
52  
53 304 the remainder of the training session. CURATE.AI intensity recommendations will be  
54  
55 305 within a pre-specified intensity range of thirteen difficulty levels. This process will be  
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306 repeated for all CURATE.AI-guided training sessions in the DI and will continue until  
 307 the end of the ten-week intervention.

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 309 **Trial Schedule and Investigations**

310 The feasibility SPIRIT trial schedule is summarised in Figure 2 and investigations are  
 311 described in detail below.

312



313  
 314 **Figure 2. Feasibility SPIRIT trial schedule and investigations**

316 Participants will undergo a combined non-digital cognitive evaluation and a 10-15-  
 317 minute DD session at time points T<sub>0</sub> to T<sub>4</sub>.

318 T<sub>0</sub>: Pre-radiotherapy combined non-digital cognitive evaluation and DD session

319 T<sub>0</sub> is a pre-radiotherapy session to evaluate cognitive function prior to radiotherapy.

320 This may not always be possible due to the short time frame between the decision to  
 321 undergo radiotherapy and its commencement. T<sub>0</sub> is a desirable timepoint, but not  
 322 essential.

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3 3234  
5 324 T<sub>1</sub>: Post-radiotherapy combined non-digital cognitive evaluation and DD session6  
7 325 T<sub>1</sub> is a post-radiotherapy and pre-DI session to evaluate baseline cognitive function8  
9 326 prior to the DI. T<sub>1</sub> is an essential timepoint.10  
11  
12 32713  
14 328 CURATE.AI COR-Tx Platform Digital Intervention (DI)15  
16 329 Participants will complete three 12-15-minute DI sessions per week (Monday,17  
18 330 Wednesday and Friday) over 10 weeks for a total of 30 sessions. The CURATE.AI19  
20 331 COR-Tx platform interface can be any of the three digital cognitive training tasks for a21  
22 332 participant. Reminders about training sessions will be regularly sent to participants23  
24 333 during the intervention from the clinical coordinator. These sessions will be completed25  
26 334 at home on tablets provided by the study team.27  
28  
29 33530  
31 336 T<sub>2</sub>: Post-CURATE.AI COR-Tx platform DI combined non-digital cognitive evaluation32  
33 337 and DD session34  
35 338 T<sub>2</sub> is a post-DI session to evaluate cognitive function after completion of the DI.36  
37 339 Additionally, semi-structured interviews exploring other feasibility outcomes detailed38  
39 340 in later sections will occur within five days of DI completion. T<sub>2</sub> is an essential timepoint.40  
41  
42 34143  
44 342 T<sub>3</sub> and T<sub>4</sub>: Post-CURATE.AI COR-Tx platform DI combined non-digital cognitive45  
46 343 evaluation and DD sessions47  
48 344 T<sub>3</sub> and T<sub>4</sub> are post-DI sessions 16 and 32 weeks after the DI, respectively. These49  
50 345 sessions evaluate mid- and long-term retention of the effect of the DI on cognitive51  
52 346 function. T<sub>3</sub> is a desirable timepoint. T<sub>4</sub> is an optional timepoint dependent on a53  
54 347 participant's patient status and condition.55  
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5 349 **Study Completion**

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8 350 After completion of data collection and preliminary data analysis for all participants, a  
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10 351 focus group meeting of all available trial team members will be held to discuss  
11  
12 352 pertinent feasibility outcomes (detailed in subsequent sections of this protocol) and the  
13  
14  
15 353 potential expansion of a future multi-site RCT.

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17 35418  
19 355 **Sample Size**

20  
21 356 We intend to recruit 15 participants for this study. As this is a feasibility clinical trial  
22  
23  
24 357 with no prior data, we did not perform formal sample size calculations. However, this  
25  
26 358 sample size is based on the number of patients that can be practically and logistically  
27  
28 359 recruited within the period of this feasibility trial that will allow for a reasonable signal  
29  
30  
31 360 to expand to a larger RCT.

32  
33 36134  
35 362 **Data collection, management and assessment**36  
37 363 **Outcomes**38  
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40 364 *Primary outcomes*

41  
42 365 The primary outcome of this trial will be the feasibility of the CURATE.AI COR-Tx  
43  
44 366 platform as both a DI and DD. Specific feasibility outcomes will be evaluated through  
45  
46  
47 367 qualitative and quantitative methods and analyses. Qualitative methods include one-  
48  
49 368 hour semi-structured patient interviews and a trial team member focus group. The  
50  
51 369 guide for the semi-structured interviews is provided in Supplemental Material 1. The  
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53  
54 370 specific aspects of feasibility, as defined by Bowen et al. to be assessed in this trial  
55  
56 371 include acceptability, demand, implementation, practicality and limited efficacy testing  
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372 [40]. Details of feasibility outcomes including definitions, measurement methods and  
373 analysis methods are provided in Table 1.

For peer review only

374 Table 1. Description of the feasibility outcomes to be assessed and how they will be collected and evaluated

Aspect of Feasibility [40]	Feasibility Outcome	Outcome Definition	Methods for Data Collection	Methods for Data Analysis	Feasibility Outcome Evaluation according to CONSORT Traffic Light System [34]		
					Green	Yellow	Red
Acceptability	Patient acceptability	Patient perceived acceptability and suitability of the DI/DD	Data collected from semi-structured interviews with patients	Thematic analysis	-	-	-
	Trial team acceptability	Trial team perceived acceptability and suitability of the DI/DD	Data collected from focus group with trial team members at end of trial	Thematic analysis	-	-	-
	Randomisation appropriateness	Patient perceived appropriateness to hypothetically being randomised into a control group in a future clinical trial	Semi-structured interviews	Thematic analysis	-	-	-
Demand	Uptake	Percentage of successfully recruited patients from all patients approached and eligible for the study	Data collected during patient recruitment	Descriptive statistics	>50%	10-50%	<10%
	Retention	Percentage of patients that complete the trial from all successfully recruited patients.	Data collected throughout trial completion. Reasons for drop-out will also be documented.	Descriptive statistics	>70%	20-70%	<20%
	Adherence (actual use)	Percentage of completed DI/DD sessions by patients at indicated timepoints	Data collected throughout trial completion	Descriptive statistics	>90%	10-90%	<10%
Implementation	Success of DI execution	Percentage of DI sessions successfully performed at the indicated timepoints within this setting	Data collected throughout trial completion	Descriptive statistics	>70%	10-70%	<10%
	Success of DD execution	Percentage of DD sessions successfully performed at the indicated timepoints within this setting	Data collected throughout trial completion	Descriptive statistics	>70%	10-70%	<10%

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	CURATE.AI degree of execution	Percentage of patients to whom we successfully apply CURATE.AI profile analysis to	Data collected throughout trial completion	Descriptive statistics	>70%	10-70%	<10%
	Compliance response	The percentage of patients requiring and responding to reminders to complete DI/DD sessions	Data collected throughout trial completion	Descriptive statistics	-	-	-
Practicality	DI/DD practicality	Trial team perception of the ability of patients to carry out DI/DD activities	Data collected from focus group with trial team members at end of trial	Thematic analysis	-	-	-
	Logistical feasibility	Logistical considerations with current trial protocol that would need to be addressed or accounted for a future RCT	Data collected from focus group with trial team members at end of trial	Thematic analysis	-	-	-
Limited-efficacy testing	DI limited efficacy	Exploratory analysis of the DI on the intended change in cognitive functioning pre-post intervention	Data collected from cognitive evaluation and DD sessions of the trial	Descriptive statistics	-	-	-
	DD limited efficacy	Exploratory correlational analysis of outcomes between the digital cognitive training task and standard-of-care, gold standard cognitive evaluations	Data collected from cognitive evaluation and DD sessions of the trial	Descriptive statistics	-	-	-

### 376 *Secondary and Exploratory Outcomes*

377 Secondary outcomes of this trial include the usability of CURATE.AI COR-Tx platform  
378 as a DI and DD in brain tumour patients post-radiotherapy. Usability will be evaluated  
379 qualitatively as part of the semi-structured interview session.

380

381 Exploratory outcomes will include the user experience (UX) of the CURATE.AI COR-  
382 Tx platform as a DI and DD in brain tumour patients post-radiotherapy. UX will be  
383 evaluated qualitatively in the semi-structured interview session. Further, as the  
384 participants will use the CURATE.AI COR-Tx platform throughout the duration of their  
385 care, it is possible that the objective, quantifiable physiological and behavioural data  
386 collected from the DTx, known as digital biomarkers, may offer the ability to detect  
387 changes in cognitive function and declines in these patients [33]. Therefore, an  
388 additional exploratory outcome will include capturing and preliminary evaluation of  
389 potential digital biomarkers for cognitive function and declines during the DI sessions.

390

### 391 Patient-Centred Outcomes

#### 392 *Cognitive Function*

393 The non-digital cognitive evaluations will be used to assess different domains of  
394 cognitive functioning including memory, verbal fluency, executive function and global  
395 function, and serve as the “gold standard” comparison to evaluate the limited efficacy  
396 of the CURATE.AI CORTx platform as a DI and DD. All combined non-digital cognitive  
397 evaluations will be performed by a clinical neuropsychologist who will administer the  
398 test battery as recommended by the Radiotherapy Oncology Group (RTOG) [41].  
399 Memory impairment will be assessed using the Hopkins Verbal Learning Test (HVLT)  
400 [42]. Verbal fluency will be assessed using the Controlled Oral Word Association Test



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3 401 (COWAT) [43]. Executive function will be assessed using the Trail Making Test (Parts  
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5 402 A and B) [44]. Global cognitive functioning will be assessed using the Mini-Mental  
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7 403 State Examination (MMSE) [45]. Patient reported health related quality of life will be  
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10 404 assessed using the SF-36 [46]. Skill transfer will be assessed using the Functional  
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12 405 Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) [47,48] and Cognitive  
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14 406 Failures Questionnaire [49]. Finally, the same clinical neuropsychologist will  
15  
16 407 administer DD session which will be recorded via the CURATE.AI COR-Tx platform.  
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18 408 Each combined non-digital cognitive evaluation and DD session will take  
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20 409 approximately one hour to complete and will be performed at the Department of  
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22 410 Radiation Oncology clinic at NCIS.  
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## 28 412 **Qualitative and Statistical Analysis**

30 413 We will perform and report descriptive and inferential statistical analyses of the  
31  
32 414 quantitative outcome measures. For qualitative outcomes thematic analysis will be  
33  
34 415 used. All interviews and focus group sessions will be recorded and transcribed  
35  
36 416 verbatim. Coding will be done manually. The analysis will follow the three stages: (1)  
37  
38 417 data will be descriptively labelled (open coding); (2) labelled data will be grouped into  
39  
40 418 categories based on literature (secondary coding); and (3) understanding the  
41  
42 419 categories to create broader themes/assertions [50]. We will not statistically analyse  
43  
44 420 exploratory outcomes.  
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## 51 422 **Data Availability**

52 423 Data generated and/or analysed during this clinical feasibility trial will be made  
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54 424 available from the corresponding author on reasonable request.  
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## 426 **Safety Monitoring and Data Storage**

### 427 Safety Monitoring

428 The clinically trained Principal Investigator (PI) will oversee and monitor the conduct  
429 of this study to ensure the health and safety of participants and the validity and integrity  
430 of the data. Participants will be fully informed of the study requirements throughout the  
431 conduct of the study and should comply with the research protocol or be allowed to  
432 withdraw from participation. The PI will notify participants of any information relevant  
433 to their continued participation. Specifically, the PI will review the research protocol,  
434 evaluate the progress of the trial, including periodic assessments of data quality and  
435 timeliness, participant recruitment, accrual and retention, participant risk versus  
436 benefit, performance of the trial site, and other factors that can affect study outcome.  
437 Scientific or therapeutic developments that may have an impact on the safety of the  
438 participants or the ethics of the study will be considered. The PI will make  
439 recommendations to the Domain Specific Review Board (DSRB) and trial site  
440 concerning continuation or conclusion of the trial. The PI will protect the confidentiality  
441 of the trial data and the results of monitoring. CURATE.AI COR-Tx will only  
442 recommend the training intensity within the pre-specified intensity.

443

### 444 Safety reporting and monitoring

445 Adverse events (AE) and serious adverse events (SAE) will be monitored and  
446 recorded. All AEs will be recorded on the patient's case report form (CRF) from date  
447 of informed consent to 30 days following the last therapy session or initiation of new  
448 therapy, whichever occurs first. All treatment-related AEs will be followed until  
449 resolution of or until initiation of new therapy, whichever occurs first. During the long-  
450 term follow-up period, only secondary malignancies will be captured as AE. For both

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3 451 AEs and SAEs, the investigator will provide a record of the start and stop dates of the  
4  
5 452 event, the action taken with study treatment as a result of the event (e.g.,  
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7 453 discontinuation or reduction of study treatment), and outcome of the event. In the event  
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10 454 of a possible study treatment-related AE, the investigator will to the best of his/her  
11  
12 455 ability assess its relationship to the study treatment. If an AE is considered serious,  
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14 456 both the AE page/screen of the CRF and the SAE Report Form will be completed.  
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### 19 458 Data Storage

21 459 Participants will interact with the CURATE.AI COR-Tx platform on trial provided  
22  
23 460 tablets. Participant-identifying information (name, contact number, email) and the data  
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25 461 linking subject identifiers and the subject identification codes will be collected and  
26  
27 462 stored on one of the laboratory password-protected computers, which are kept in  
28  
29 463 locked office rooms by the clinical team, separately from the research data to ensure  
30  
31 464 that participants cannot be individually matched to their data. Clinical data will be  
32  
33 465 stored on the Research Electronic Data Capture (REDCap) platform, a secure web  
34  
35 466 application for building and managing online databases compliant with 21 Code of  
36  
37 467 Federal Regulations (CFR) Part 11, Federal Information Security Management Act  
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39 468 (FISMA), Health Insurance Portability and Accountability Act (HIPAA) and General  
40  
41 469 Data Protection Regulation (GDPR), purposefully built to support online and offline  
42  
43 470 data capture for research. While the study is ongoing, the de-identified (coded)  
44  
45 471 research data will be retrieved from REDCap by the data analysis team and stored on  
46  
47 472 one of the laboratory password-protected computers, which are kept in locked office  
48  
49 473 rooms. Participants will be provided with a unique account and password to access  
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51 474 sessions on the CURATE.AI COR-Tx platform. Only their own performance data will  
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53 475 be stored within their unique account and on the secure cloud platform. Only the  
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3 476 technical team will have access to the CURATE.AI COR-Tx platform performance  
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5 477 data. Only the PI and collaborators will have access to the de-identified trial data.  
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10 479 Audio recordings and transcripts (with no identifiers revealed) of the semi-structured  
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12 480 interviews will be coded and stripped of identifying information at the earliest  
13  
14 481 opportunity to ensure confidentiality of the participants. Participant-identifying  
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16 482 information will be discarded upon the completion of the research. Research data will  
17  
18 483 be kept for future meta-analyses (including power analyses) and other occasions when  
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20 484 the original data need to be referenced. These data will be retained for at least 10  
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22 485 years.  
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### 27 28 487 **Patient and Public Involvement**

29  
30 488 This feasibility clinical trial was designed without patient and public involvement.  
31  
32 489 However, this feasibility clinical trial includes a mixed-methods approach including  
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34 490 semi-structured patient participant interviews with aims to explore acceptability,  
35  
36 491 usability and user experience of the CURATE.AI COR-Tx platform as a DI and DD.  
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38 492 The valuable input we will receive from these patient participants will be incorporated  
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40 493 into the design of a future RCT.  
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### 45 46 495 **Ethics and dissemination**

47  
48 496 This study has been approved by the National Healthcare Group (NHG) DSRB,  
49  
50 497 reference: DSRB2020/00249. Clinical investigators will explain the protocol and obtain  
51  
52 498 written, informed consent from patients as per the protocol prior to taking part in the  
53  
54 499 study. We will report our findings at scientific conferences and/or in peer-reviewed  
55  
56 500 journals. We will not publish any personal health identifiers.  
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## Author Statements

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### Author contributions

XT, AB, TK, DC, CLA, DH and BAV developed the study concept and initiated the project. AR, XT, GNSK, AB, TK, SV, LN, MR, WTDC, CLA, DH and BAV provided significant input into the development of the protocol. AR, SV, MR, QYC, FA, TKJ, YTT, AW, WTDC and BAV will implement the protocol and oversee the collection of the data. AR and XT drafted the manuscript, and all authors (AR, XT, GNSK, AB, TK,

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3 SV, LN, MR, QYC, FA, YR, TKJ, YTT, AW, WTDC, CLA, DH and BAV) read,  
4  
5 contributed to and approved the final manuscript.  
6  
7

### 8 9 **Competing interests**

10  
11 AB, TK, CLA and DH are co-inventors of previously filed pending patents on artificial  
12  
13 intelligence-based therapy development. DH and TK are shareholders of KYAN  
14  
15 Therapeutics, which has licensed intellectual property pertaining to AI-based  
16  
17 oncology drug development and personalised medicine.  
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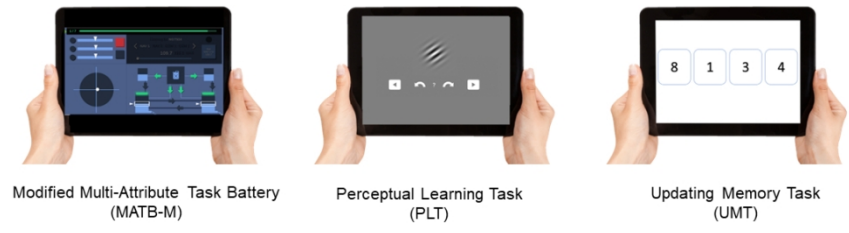


Figure 1. CURATE.AI COR-Tx platform digital cognitive training tasks  
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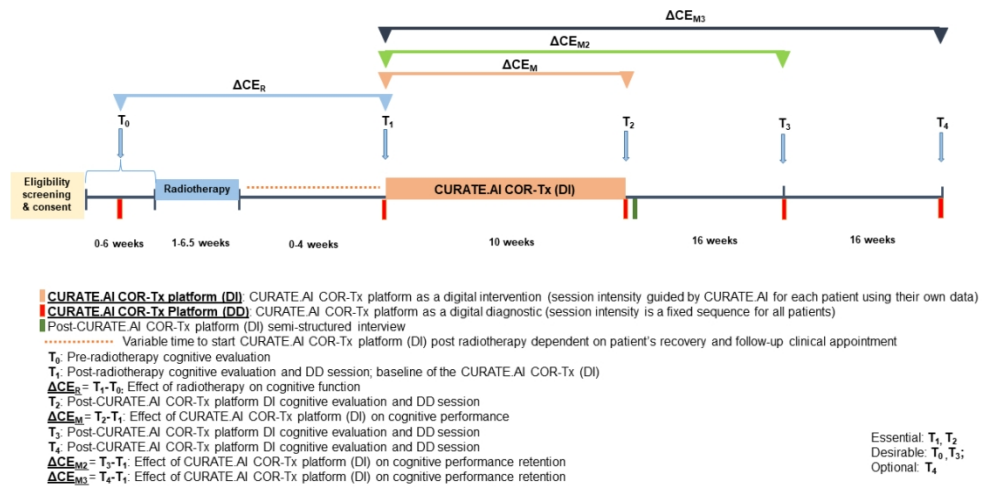


Figure 2. Feasibility SPIRIT trial schedule and investigations

855x481mm (38 x 38 DPI)

## Voluntary Interview Guide

### Demographic Details

- Age
- Gender
- Education
- Occupation
- Clinical status

### Theme 1: Project objective (Why the choice?)

- Could you tell us why you decided to participate in the study?
- What are you trying to achieve/what are your expectations?
- What are some alternatives you may try instead of this? And why?
- What do you feel about the interface/intervention?
- What were you looking for when you were informed of such a project?
- What do you feel about the instructions?
- Could you comment on this method of training/evaluation?
- Do you think it's appropriate to be randomised into a control group in a future clinical trial?

### Theme 2: Overall experience (What facilitates and what hinders?)

- What do you like about the interface/intervention?
- What don't you like?
- Is there something you've done previously that's similar?
- Would you know anyone who might enjoy this interface?- Could you describe those people?
- What is your opinion on the time taken- Overall, task wise?
- What are your thoughts about the doctor's absence in this?
- How confident do you feel using the interface?
- Did you face difficulties? Could you elaborate?
- What was easy in do in this?
- What is good about this? What isn't?
- Would you voluntarily do it?
- Is this something you would like as part of your formal treatment?
- How would you like to use it- the medium, ideas on the interface?
- Do you think there were or there could be any adverse events in this?

### Theme 3: Training (How do you help people to use the interface?)

- What did you learn?
- How did it help?
- What could have been better?
- How was the explanation/instructions?



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Abstract/Title Page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract/Title Page/Methods/Analyses
	2b	All items from the World Health Organization Trial Registration Data Set	_____ NA _____
Protocol version	3	Date and version identifier	_____ NA _____
Funding	4	Sources and types of financial, material, and other support	Funding Statement
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page/Author contribution statement
	5b	Name and contact information for the trial sponsor	_____ NA _____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Funding Statement



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5d Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

**Introduction**

- Background and rationale 6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention Introduction
- 6b Explanation for choice of comparators Introduction
- Objectives 7 Specific objectives or hypotheses Introduction
- Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Trial Design

**Methods: Participants, interventions, and outcomes**

- Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Trial Design
- Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) Study Setting and Participants
- Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Intervention
- 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) Safety Monitoring
- 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) CURATE.AI COR-Tx Platform Digital Intervention (DI)

1		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____NA_____
2	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Outcomes
3				
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8	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Trial Schedule and Investigations
9				
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11	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Sample Size
12				
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15	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____NA_____
16				
17	<b>Methods: Assignment of interventions (for controlled trials)</b>			
18	<b>Allocation:</b>			
19				
20	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____NA_____
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27	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____NA_____
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31	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____NA_____
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35	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____NA_____
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38		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____NA_____
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1 **Methods: Data collection, management, and analysis**

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3 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related Outcomes

4 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a

5 description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and

6 validity, if known. Reference to where data collection forms can be found, if not in the protocol

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9 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be \_\_\_\_\_ - \_\_\_\_\_

10 collected for participants who discontinue or deviate from intervention protocols

11

12 Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote data Data Management

13 quality (eg, double data entry; range checks for data values). Reference to where details of data

14 management procedures can be found, if not in the protocol

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17 Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of Qualitative and

18 the statistical analysis plan can be found, if not in the protocol Statistical Analysis/

19 Table 1

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21 20b Methods for any additional analyses (eg, subgroup and adjusted analyses) \_\_\_\_\_ NA \_\_\_\_\_

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23 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and

24 any statistical methods to handle missing data (eg, multiple imputation) \_\_\_\_\_ NA \_\_\_\_\_

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27 **Methods: Monitoring**

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29 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; \_\_\_\_\_ NA \_\_\_\_\_

30 statement of whether it is independent from the sponsor and competing interests; and reference to

31 where further details about its charter can be found, if not in the protocol. Alternatively, an explanation

32 of why a DMC is not needed

33

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35 21b Description of any interim analyses and stopping guidelines, including who will have access to these Safety Monitoring

36 interim results and make the final decision to terminate the trial

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38 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse Safety Monitoring

39 events and other unintended effects of trial interventions or trial conduct

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1	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____NA_____
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4	<b>Ethics and dissemination</b>			
5				
6	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Ethics and dissemination
7				
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9	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____ - _____
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14	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Consent Procedure
15				
16				
17		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Consent Procedure
18				
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20	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Data Management
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23	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Declarations of Interest
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27	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Data management
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30	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____NA_____
31				
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33	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____22_____
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38		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ - _____
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40		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ - _____
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**Appendices**

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____ ICF _____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____ - _____

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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

peer review only

# BMJ Open

## **CURATE.AI COR-Tx platform as a digital therapy and digital diagnostic for cognitive function in brain tumour patients post-radiotherapy treatment: Protocol for a prospective mixed-methods feasibility clinical trial**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-077219.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Sep-2023
Complete List of Authors:	Remus, Alexandria; N.1 Institute for Health; Heat Resilience and Performance Centre, Yong Loo Lin School of Medicine Tadeo, Xavier; N.1 Institute for Health Kai, Grady Ng Shi; NUS, Department of Social Sciences Blasiak, Agata; N.1 Institute for Health Kee, Theodore; N.1 Institute for Health; National University of Singapore, Department of Biomedical Engineering Vijayakumar, Smrithi; N.1 Institute for Health Nguyen, Le; N.1 Institute for Health; National University of Singapore, Department of Biomedical Engineering Raczkowska, Marlena; N.1 Institute for Health Chai, Qian Yee; National University Hospital, Department of Radiation Oncology Aliyah, Fatin; National University Hospital, Department of Radiation Oncology Rusalovski, Yaromir; N.1 Institute for Health Jia, Teo Ke; National University Hospital, Department of Surgery Yeo, Tseng Tsai; National University Hospital, Department of Surgery, Division of Neurosurgery WONG, Andrea Li Ann; National University Health System Chia, David; National University Health System, Radiation Oncology Asplund, Christopher L.; National University of Singapore; NUS, Department of Social Sciences Ho, Dean; N.1 Institute for Health; National University of Singapore, Department of Biomedical Engineering Vellayappan, Balamurugan A.; National University of Singapore; National University Hospital, Department of Radiation Oncology
<b>Primary Subject Heading</b>:	Rehabilitation medicine
Secondary Subject Heading:	Neurology, Oncology, Patient-centred medicine, Pharmacology and therapeutics, Qualitative research
Keywords:	RADIOTHERAPY, Clinical Trial, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, Feasibility Studies

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4 **cognitive function in brain tumour patients post-radiotherapy treatment:**  
5 **Protocol for a prospective mixed-methods feasibility clinical trial**  
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peer review only

## 1 **ABSTRACT**

### 2 **Introduction**

3 Conventional interventional modalities for preserving or improving cognitive function  
4 in brain tumour patients undergoing radiotherapy usually involve pharmacological  
5 and/or cognitive rehabilitation therapy administered at fixed doses or intensities, often  
6 resulting in sub-optimal or no response, due to the dynamically evolving patient state  
7 over the course of disease. The personalisation of interventions may result in more  
8 effective results for this population. We have developed the CURATE.AI COR-Tx  
9 platform, which combines a previously validated, artificial intelligence-derived  
10 personalised dosing technology with digital cognitive training.

### 12 **Methods and analysis**

13 This is a prospective, single-centre, single-arm, mixed-methods feasibility clinical trial  
14 with the primary objective of testing the feasibility of the CURATE.AI COR-Tx platform  
15 intervention as both a digital intervention and digital diagnostic for cognitive function.  
16 Fifteen patient participants diagnosed with a brain tumour requiring radiotherapy will  
17 be recruited. Participants will undergo a remote, home-based 10-week personalised  
18 digital intervention using the CURATE.AI COR-Tx platform three times a week.  
19 Cognitive function will be assessed via a combined non-digital cognitive evaluation  
20 and a digital diagnostic session at five time points: pre-radiotherapy, pre- and post-  
21 intervention and 16- and 32-weeks post-intervention. Feasibility outcomes relating to  
22 acceptability, demand, implementation, practicality and limited efficacy testing as well  
23 as usability and user experience will be assessed at the end of the intervention through  
24 semi-structured patient interviews and a study team focus group discussion at study  
25 completion. All outcomes will be analysed quantitatively and qualitatively.

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3 26  
45 27 **Ethics and Dissemination**

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7  
8 28 This study has been approved by the National Healthcare Group (NHG) DSRB  
9  
10 29 (DSRB2020/00249). We will report our findings at scientific conferences and/or in  
11  
12 30 peer-reviewed journals.  
13

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15 3116  
17 32 **Trial registration**18  
19 33 NCT04848935  
20  
21 3422  
23  
24 35 **Keywords**

25  
26 36 Digital therapeutics, artificial intelligence, brain tumour, radiotherapy, feasibility,  
27  
28 37 personalised medicine, cognitive rehabilitation, clinical trial  
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30 38

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32  
33 39 **Word Count**34  
35 40 4300  
36  
37 4138  
39  
40 42 **Strengths and limitations of this study**

- 41  
42 43 • This is a prospective, mixed-methods feasibility trial to inform a future clinical  
43  
44 44 trial.  
45  
46 47 • The behavioural component will provide insights into how to further develop  
47  
48 46 the intervention for the patient population as well as how to scale for a larger  
49  
50 47 multisite randomised control by including patients and study team members  
51  
52 48 (clinicians/data team members).  
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3 49 • This feasibility trial is a model for a decentralised trial in which patients can  
4  
5 50 undergo treatment in the comforts of their own home and clinicians can  
6  
7 51 monitor their progress.  
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9  
10 52 • The non-randomised single-arm feasibility trial does not simulate a  
11  
12 53 randomised control trial as closely as a randomised pilot and is limited in  
13  
14 54 informing on issues that may arise from the logistical process on a larger  
15  
16 55 scale, including future decisions on determining eligibility criteria from a  
17  
18 56 diverse patient population.  
19  
20  
21 57 • The digital nature of this intervention requires a higher level of technological  
22  
23 58 literacy and skills which may be intimidating to some, introducing potential  
24  
25 59 bias in recruitment and may have limited generalisability to other countries  
26  
27 60 owing to cultural differences.  
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## 61 INTRODUCTION

62 Patients with brain tumours who undergo radiotherapy exhibit cognitive impairments  
63 throughout the course of their condition. These impairments often include decline in  
64 memory, attention and executive function, and they can be attributed to the tumour  
65 itself and/or side effects of its treatment [1–5]. Cognitive deficits are reported to occur  
66 before radiotherapy treatment and in between 50-90% of adult patients six months  
67 after treatment [1,6–8]. Such high prevalence, coupled with the increase in life  
68 expectancy of brain tumour patients necessitates the need for appropriate strategies  
69 that preserve and improve cognitive functioning in brain tumour survivors.

70  
71 To date, pharmacological interventions and cognitive rehabilitation therapy (CRT)  
72 have been the main approaches used to preserve and improve cognitive functioning  
73 in these patients [1]. Pharmacological interventions typically include repurposed  
74 medications for cognitive functioning in other conditions, such as donepezil,  
75 armodafinil, modafinil and methylphenidate [1]. However, evidence of the efficacy of  
76 these pharmacological interventions is limited and trial endpoints are often unmet [1,9–  
77 12]. CRT involves neuropsychological interventions that are meant to augment various  
78 domains of cognitive function through the mechanism of neuroplasticity [1]. CRTs can  
79 be provided directly to an individual or in group settings, conducted at home or in  
80 dedicated rehabilitation centres, and delivered face-to-face by a qualified clinician as  
81 pen-and-paper exercises or through computerised programmes [1]. CRTs have shown  
82 promise with improvements in desired cognitive performance reported after their use  
83 in some patients [1,9,13]. However, these findings are limited and inconsistently  
84 reported across studies, warranting further development of more robust CRTs for this  
85 population.

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3 86 In both the pharmacological and CRT modalities, the reported treatment regimens are  
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5 87 typically administered as a one-size-fits-all intervention with fixed doses or training  
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7 88 intensities for the duration of the treatment for all patients. However, not only does the  
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10 89 state of patient typically evolve over the duration of their condition, but each patient  
11  
12 90 also experiences variable factors, such as tumour burden (e.g., size, position, and  
13  
14 91 type), baseline cognitive abilities, treatment type and response (e.g., efficacy, side  
15  
16 92 effects, etc.). As such, it remains possible that these uniform one-size-fits-all, fixed  
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18  
19 93 dose interventions are a large contributing factor to the sub-optimal responses  
20  
21 94 experienced by some patients [14]. To be more effective, interventions that aim to  
22  
23 95 preserve and improve cognitive functioning should treat each patient as an individual  
24  
25  
26 96 case, with the treatment tailored to that individual. Therefore, there is an urgent need  
27  
28 97 to develop therapies that are personalised and that can dynamically adapt throughout  
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30  
31 98 the course of the condition for brain tumour patients that undergo radiotherapy.  
32  
33 99 Recently, artificial intelligence (AI) has established itself as a paradigm-shifting  
34  
35 100 technology in healthcare with the potential to transform many aspects of patient care,  
36  
37 101 if used appropriately [15]. In particular, AI shows great potential in personalising care  
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40 102 for patients from diagnosis to treatment selection and optimising intervention [14,16].  
41  
42 103 As such, integrating AI into CRTs is a plausible solution to overcome the  
43  
44 104 aforementioned challenges and pitfalls of the current one-size-fits-all, fixed dose  
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46  
47 105 interventions.

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49 106  
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51 107 Commonly, AI health technologies are developed from the big data paradigm in which  
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53 108 population data and advanced statistical analyses are harnessed to diagnose and treat  
54  
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56 109 individual patients based on their demographics and disease history [17]. These are  
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58 110 often highly successful, but require large population datasets and substantial prior  
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3 111 knowledge of the targeted condition in order to personalise care and avoid common  
4  
5 112 biases [14,16,18]. Further, while these methods can account for inter-patient variability  
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8 113 to identify appropriate care strategies, they have limited ability to account for the intra-  
9  
10 114 patient variability of a dynamically changing patient state throughout the course of their  
11  
12 115 condition [14]. In contrast to the big data paradigm, small data paradigm AI health  
13  
14 116 technologies framed to serve N-of-1 medicine require as little as only a patient's own  
15  
16 117 data to deliver personalised care by rapidly capturing their own response to a  
17  
18 118 treatment over time [14,16,19,20]. AI for N-of-1 medicine may be a favourable  
19  
20 119 approach to dynamically modulate an intervention with the goal of optimising the  
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22 120 efficacy for a patient over time [19]; and therefore has potential to improve  
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24 121 interventions aimed at preserving and improving cognitive function in brain tumour  
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26 122 patients.  
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33 124 CURATE.AI is a small data, AI-derived, indication-agnostic and mechanism-  
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35 125 independent platform that maps the relationship between an intervention intensity  
36  
37 126 input and the phenotypic response output for a patient, using exclusively their own  
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39 127 data [21]. It is based on a previously established observation that a quadratic surface  
40  
41 128 can closely represent the relationship between varying intervention intensities input  
42  
43 129 and measurable phenotypic response output in a human system [22–27]. Using this  
44  
45 130 premise, the platform is prospectively calibrated by correlating patient-specific  
46  
47 131 responses to a range of intervention intensities to create a patient's individualised  
48  
49 132 CURATE.AI profile. The prospectively calibrated profile is then paired with an intensity  
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51 133 optimisation process to predict the patient's phenotypic response output for a specified  
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53 134 intensity input and to provide treatment intensity recommendations for optimised  
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3 135 results. Importantly, the individualised CURATE.AI profile can be continuously  
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5 136 recalibrated as the patient evolves throughout the course of their condition.  
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10 138 To date, the validity of CURATE.AI has been successfully demonstrated, both  
11  
12 139 retrospectively and prospectively, for single drug optimisation of immunosuppression  
13  
14 140 therapy [28] and for combination drug optimisation of oncology therapy [29,30]. Most  
15  
16 141 recently, CURATE.AI was demonstrated as an integral part of a cognitive training  
17  
18 142 platform to derive individualised learning profiles for young adults [31]. More  
19  
20 143 specifically, in the prospective, proof-of-concept study, the CURATE.AI platform was  
21  
22 144 used to derive personalised learning profiles of healthy participants while they  
23  
24 145 completed a multitasking cognitive training paradigm. The personalised learning  
25  
26 146 profiles were generated by correlating a participant's performance improvement to  
27  
28 147 their performance at various intensities of the multitasking cognitive training paradigm.  
29  
30  
31 148 Overall, these profiles revealed substantial differences between individual  
32  
33 149 performance at various intensity levels and demonstrated that individual-specific  
34  
35 150 exposure to different training intensities is required to achieve maximum performance  
36  
37 151 improvement during the multitasking cognitive training paradigm. The ability of the  
38  
39 152 CURATE.AI platform to identify individualised training profiles provides the foundation  
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41 153 for the optimisation of non-pharmaceutical therapies, such as CRTs.  
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49 154  
50 155 Therefore, to address the urgent clinical need for a dynamic, personalised therapy that  
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52 156 is effective in preserving and improving cognitive functioning in brain tumour patients  
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54 157 who undergo radiotherapy, we have developed the CURATE.AI COR-Tx platform as  
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56 158 a digital therapeutic (DTx) with the potential to be used as a treatment and diagnostic  
57  
58 159 tool. DTx are evidence-based software programmes that prevent, manage or treat a  
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3 160 medical condition or disease that can be used independently or together with other  
4  
5 161 modalities to deliver care directly to patients [32]. DTx are typically easily deployable  
6  
7 162 for at-home use and efficacy measurements (e.g., scoring) can be given back to the  
8  
9 163 individual as feedback. both of which may contribute to improved patient compliance  
10  
11 164 and efficacy [16]. The CURATE.AI COR-Tx platform combines CURATE.AI with tablet-  
12  
13 165 ready digital cognitive training tasks as the interface. The CURATE.AI COR-Tx  
14  
15 166 platform can dynamically optimise the treatment for the entire duration a patient's care.  
16  
17 167 This may result in improved cognitive function in these patients, as compared to  
18  
19 168 traditional one-size-fits all, fixed-intensity CRTs, and potentially serve as an effective,  
20  
21 169 interventional modality for brain tumour patients that undergo radiotherapy. Further,  
22  
23 170 as the CURATE.AI COR-Tx platform can be used throughout the duration of the  
24  
25 171 condition, from initial diagnosis to after radiotherapy treatment, it is possible that  
26  
27 172 performance measures captured by the digital cognitive training tasks may have the  
28  
29 173 capacity to remotely establish cognitive function levels by detecting and monitoring a  
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31 174 patient's own ability and changes at dedicated time points and over time.  
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## 40 176 **Objectives**

41  
42 177 The primary objective of this trial is to test the feasibility of the CURATE.AI COR-Tx  
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44 178 platform as a digital intervention (DI) and a digital diagnostic (DD) for cognitive function  
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46 179 in post-radiotherapy brain tumour patients. The secondary objective of this trial is to  
47  
48 180 assess the usability of the CURATE.AI COR-Tx platform. Further exploratory  
49  
50 181 objectives are to assess user experience (UX) with the CURATE.AI COR-Tx platform.  
51  
52 182 Additionally, as the participants will use the CURATE.AI COR-Tx platform throughout  
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54 183 the duration of their care, it is possible that the objective, quantifiable physiological  
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56 184 and behavioural data collected from the DTx, known as digital biomarkers, may offer  
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3 185 the ability to detect changes in cognitive function, such as improvement or decline, in  
4  
5 186 these participants [33]. Therefore, an additional exploratory outcome will include  
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7 187 capturing and preliminary evaluation of potential digital biomarkers for cognitive  
8  
9 188 function during the DI sessions. The results of this clinical feasibility trial will provide  
10  
11 189 data required to design a definitive future multi-site randomised control trial (RCT) to  
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13 190 assess the efficacy of the CURATE.AI COR-Tx platform.  
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## 192 **METHODS AND ANALYSIS**

193 This trial is registered and published at ClinicalTrials.gov (NCT04848935). This  
194 protocol was prepared in adherence to the Consolidated Standards of Reporting  
195 Trials (CONSORT) extension for randomised pilot and feasibility trials reporting  
196 guidelines [34] and Standard Protocol Items: Recommendations for Interventional  
197 Trials (SPIRIT) [35].  
198

198

### 199 **Trial design**

200 This is a prospective, single-centre, single-arm, mixed-methods feasibility clinical trial.  
201 The start date for this study was in April 2021 and is expected to run until April 2024.  
202 The outcome of this trial will provide data required to design a definitive, future, multi-  
203 site RCT. Criteria for progression to a future larger trial will be based on the combined  
204 qualitative and quantitative feasibility of primary and secondary outcomes.  
205

205

### 206 **Study setting and participants**

207 Fifteen patient participants will be recruited from the Department of Radiation  
208 Oncology, National University Cancer Institute Singapore (NCIS), part of the National  
209 University Health System (NUHS) in Singapore. Clinical investigators will recruit  
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3 210 patients according to eligibility requirements during routine clinical visits prior to the  
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5 211 planned commencement of partial or whole brain radiotherapy. Written informed  
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7 212 consent will be gained from each participant prior to inclusion in this study. The rolling  
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9 213 recruitment period for this study is between May 2021 and July 2023. Participants that  
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11 214 are removed or drop out will not be replaced.  
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### 16 216 **Eligibility criteria**

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19 217 Inclusion criteria: Patient participants (1) with a neoplastic condition (benign or  
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21 218 malignant) involving the brain or skull requiring radiotherapy (with or without  
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23 219 chemotherapy); (2) aged  $\geq 21$  years; (3) Eastern Cooperative Oncology Group  
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25 220 (ECOG) Performance Status of 0 to 2; and (4) with a life expectancy of at least six  
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27 221 months.  
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33 223 Exclusion criteria: Patient participants (1) undergoing stereotactic radiosurgery (single  
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35 224 fraction); (2) undergoing re-irradiation to the same area of the brain; (3) unable to give  
36  
37 225 informed consent; (4) who cannot understand spoken English language; (5) physically  
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39 226 incapable of using a computer tablet (either due to vision loss or dominant hand  
40  
41 227 weakness); and (6) who are pregnant or breastfeeding women.  
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### 46 229 **Consent Procedure**

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49 230 The lead clinical coordinator will meet potential participants at their outpatient  
50  
51 231 appointment where they will be provided with a consent form, participant information  
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53 232 leaflet and a verbal explanation of the study. Participants who are willing to take part  
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55 233 in the study will sign a consent form and an appointment for baseline testing prior to  
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3 234 commencement of their radiotherapy treatment will be scheduled (Supplemental  
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5 235 Material 1).  
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10 237 **Intervention**

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12 238 CURATE.AI COR-Tx Platform

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14 239 The CURATE.AI COR-Tx platform involves in-house developed tablet adaptations of  
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17 240 multitasking, perceptual learning and executive processing digital cognitive training  
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19 241 tasks which serve as the interface of the DI and DD. In the DI, the intensity of each  
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21 242 task will be independently modulated by CURATE.AI, described in detail in  
22  
23 243 subsequent sections, resulting in a dynamically personalised DTx CRT for each user.  
24  
25 244 In the DD, the intensity of each task will be fixed and predefined for all users. One or  
26  
27 245 more of the digital cognitive training tasks may serve as the interface for the  
28  
29 246 CURATE.AI COR-Tx DI or DD. The digital cognitive training tasks of the CURATE.AI  
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31 247 COR-Tx platform are depicted in Figure 1 and described in detail below.  
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37 249 *[Figure 1 about here]*

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41  
42 251 *Modified Multi-Attribute Test Battery*

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44 252 The Multi-Attribute Test Battery (MATB) is a flight deck simulator originally developed  
45  
46 253 by the National Aeronautics and Space Administration [36] and further redefined by  
47  
48 254 the United States Air Force [37]. MATB is a multitasking paradigm that requires users  
49  
50 255 to respond to the demands of four tasks simultaneously. The tasks require users to  
51  
52 256 respond to auditory commands, track a target with a joystick, monitor system gauges  
53  
54 257 for deviant readings and problem-solve to maintain fuel levels. The software was  
55  
56 258 originally developed to be played on a computer with a monitor, joystick and  
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3 259 headphones. In this current trial, participants will use a modified version of MATB  
4  
5 260 (MATB-M) that our research team has developed. MATB-M is a tablet-ready,  
6  
7 261 modernised and gamified adaptation of MATB that allows for remote operation (Figure  
8  
9 262 1). MATB-M still replicates the functionality of MATB without the auditory command  
10  
11 263 task and requires a user to complete multiple subtasks simultaneously. The intensity,  
12  
13 264 or difficulty, of each subtask within MATB-M can be modulated, primarily by adjusting  
14  
15 265 the frequency of critical events that demand evaluation and/or response. Performance  
16  
17 266 is measured by a composite score of accuracies and reaction times in event solving  
18  
19 267 of the individual tasks.  
20  
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268

#### 269 Perceptual Learning Task

270 The perceptual learning task (PLT) is an online adaption of the orientation  
271 discrimination task with Gabor patches from Lengyel & Fiser (2019) (Figure 1) [38].  
272 Users are first shown a reference Gabor patch followed by a modified test Gabor patch  
273 that may be oriented clockwise or counter-clockwise. Users are required to indicate  
274 the direction of rotation. Difficulty can be adjusted by changing the degree of similarity  
275 between the two stimuli or by changing the stimuli's visual contrast levels.  
276 Performance is measured by the accuracy of correct discriminations.  
277

278

#### 279 Updating Memory Task

280 The updating memory task (UMT) is an online adaptation of the number memory task  
281 protocol from Morris & Jones (1990) (Figure 1) [39]. In this task, a list of several  
282 numbers or letters will be presented serially for a designated time per item. Users are  
required to recall the last four items presented in the list. Difficulty can be adjusted by

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3 283 increasing the length of the list of items presented. Performance is measured by the  
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5 284 accuracy of correctly recalled sequences.  
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10 286 **CURATE.AI**

11  
12 287 CURATE.AI in this context refers to the CURATE.AI software used in the backend of  
13  
14 288 the CURATE.AI COR-Tx platform that generates the calibrated, individualised profiles  
15  
16 289 and subsequent training intensity recommendations for a DI training session. The  
17  
18 290 Health Sciences Authority in Singapore classifies CURATE.AI as a Class B medical  
19  
20 291 device (low to moderate risk), which is defined as all active therapeutic devices that  
21  
22 292 are software, or which are intended to administer or exchange energy to, or with the  
23  
24 293 human body. We have filed the accompanying Clinical Research Materials notification  
25  
26 294 (CRM-N) under the National University of Singapore, for the intended purpose of  
27  
28 295 providing training intensity recommendations within this clinical feasibility trial.  
29  
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33 296

34  
35 297 *CURATE.AI recommendation*

36  
37 298 CURATE.AI will be used to provide training intensity recommendations for the DI  
38  
39 299 component of the CURATE.AI COR-Tx platform. In CURATE.AI-guided training  
40  
41 300 sessions, for each participant, CURATE.AI will undergo an initial calibration period  
42  
43 301 with the aim of generating a personalised profile based on the treated participant's  
44  
45 302 own data only. During this initial calibration period, CURATE.AI will provide calibration-  
46  
47 303 intent training recommendations to collect data on the participant's phenotypic  
48  
49 304 response, as measured by their performance, to a range of training intensities on a  
50  
51 305 given DI task. CURATE.AI will then provide dynamic intensity recommendations for  
52  
53 306 the remainder of the training session. CURATE.AI intensity recommendations will be  
54  
55 307 within a pre-specified intensity range of thirteen difficulty levels. This process will be  
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3 308 repeated for all CURATE.AI-guided training sessions in the DI and will continue until  
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5 309 the end of the ten-week intervention.  
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### 9 10 311 **Trial Schedule and Investigations**

11  
12 312 The feasibility SPIRIT trial schedule is summarised in Figure 2 and investigations are  
13  
14 313 described in detail below.  
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17 314

18  
19 315 *[Figure 2 about here]*  
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22 316

23  
24 317 Participants will undergo a combined non-digital cognitive evaluation and a 10-15-  
25  
26 318 minute DD session at time points  $T_0$  to  $T_4$ .  
27  
28

29 319

30 320  $T_0$ : Pre-radiotherapy combined non-digital cognitive evaluation and DD session

31  
32 321  $T_0$  is a pre-radiotherapy session to evaluate cognitive function prior to radiotherapy.

33  
34 322 This may not always be possible due to the short time frame between the decision to  
35  
36 323 undergo radiotherapy and its commencement.  $T_0$  is a desirable timepoint, but not  
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38 324 essential.  
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43 326  $T_1$ : Post-radiotherapy combined non-digital cognitive evaluation and DD session

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45 327  $T_1$  is a post-radiotherapy and pre-DI session to evaluate baseline cognitive function  
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47 328 prior to the DI.  $T_1$  is an essential timepoint.  
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52 330 CURATE.AI COR-Tx Platform Digital Intervention (DI)

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54 331 Participants will complete three 12-15-minute DI sessions per week (Monday,

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56 332 Wednesday and Friday) over 10 weeks for a total of 30 sessions. The CURATE.AI  
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3 333 COR-Tx platform interface can be any of the three digital cognitive training tasks for a  
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5 334 participant. Reminders about training sessions will be regularly sent to participants  
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8 335 during the intervention from the clinical coordinator. These sessions will be completed  
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10 336 at home on tablets provided by the study team.

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14 338 T<sub>2</sub>: Post-CURATE.AI COR-Tx platform DI combined non-digital cognitive evaluation  
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16 339 and DD session

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19 340 T<sub>2</sub> is a post-DI session to evaluate cognitive function after completion of the DI.  
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21 341 Additionally, semi-structured interviews exploring other feasibility outcomes detailed  
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23 342 in later sections will occur within five days of DI completion. T<sub>2</sub> is an essential timepoint.  
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28 344 T<sub>3</sub> and T<sub>4</sub>: Post-CURATE.AI COR-Tx platform DI combined non-digital cognitive  
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30 345 evaluation and DD sessions

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32 346 T<sub>3</sub> and T<sub>4</sub> are post-DI sessions 16 and 32 weeks after the DI, respectively. These  
33  
34 347 sessions evaluate mid- and long-term retention of the effect of the DI on cognitive  
35  
36 348 function. T<sub>3</sub> is a desirable timepoint. T<sub>4</sub> is an optional timepoint dependent on a  
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38 349 participant's patient status and condition.  
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42 351 **Study Completion**

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46 352 After completion of data collection and preliminary data analysis for all participants, a  
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48 353 focus group meeting of all available trial team members will be held to discuss  
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50 354 pertinent feasibility outcomes (detailed in subsequent sections of this protocol) and the  
51  
52 355 potential expansion of a future multi-site RCT.  
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58 357 **Sample Size**  
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3 358 We intend to recruit 15 participants for this study. As this is a feasibility clinical trial  
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5 359 with no prior data, we did not perform formal sample size calculations. However, this  
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8 360 sample size is based on the number of patients that can be practically and logistically  
9  
10 361 recruited within the period of this feasibility trial that will allow for a reasonable signal  
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12 362 to expand to a larger RCT.  
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## 17 364 **Data collection, management and assessment**

### 19 365 Outcomes

#### 22 366 *Primary outcomes*

23  
24 367 The primary outcome of this trial will be the feasibility of the CURATE.AI COR-Tx  
25  
26 368 platform as both a DI and DD. Specific feasibility outcomes will be evaluated through  
27  
28 369 qualitative and quantitative methods and analyses. Qualitative methods include one-  
29  
30 370 hour semi-structured patient interviews and a trial team member focus group. The  
31  
32 371 guide for the semi-structured interviews is provided in Supplemental Material 2. The  
33  
34 372 specific aspects of feasibility, as defined by Bowen et al. to be assessed in this trial  
35  
36 373 include acceptability, demand, implementation, practicality and limited efficacy testing  
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38 374 [40]. Details of feasibility outcomes including definitions, measurement methods and  
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40 375 analysis methods are provided in Table 1.  
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376 Table 1. Description of the feasibility outcomes to be assessed and how they will be collected and evaluated

Aspect of Feasibility [40]	Feasibility Outcome	Outcome Definition	Methods for Data Collection	Methods for Data Analysis	Feasibility Outcome Evaluation according to CONSORT Traffic Light System [34]		
					Green	Yellow	Red
Acceptability	Patient acceptability	Patient perceived acceptability and suitability of the DI/DD	Data collected from semi-structured interviews with patients	Thematic analysis	-	-	-
	Trial team acceptability	Trial team perceived acceptability and suitability of the DI/DD	Data collected from focus group with trial team members at end of trial	Thematic analysis	-	-	-
	Randomisation appropriateness	Patient perceived appropriateness to hypothetically being randomised into a control group in a future clinical trial	Semi-structured interviews	Thematic analysis	-	-	-
Demand	Uptake	Percentage of successfully recruited patients from all patients approached and eligible for the study	Data collected during patient recruitment	Descriptive statistics	>50%	10-50%	<10%
	Retention	Percentage of patients that complete the trial from all successfully recruited patients.	Data collected throughout trial completion. Reasons for drop-out will also be documented.	Descriptive statistics	>70%	20-70%	<20%
	Adherence (actual use)	Percentage of completed DI/DD sessions by patients at indicated timepoints	Data collected throughout trial completion	Descriptive statistics	>90%	10-90%	<10%
Implementation	Success of DI execution	Percentage of DI sessions successfully performed at the indicated timepoints within this setting	Data collected throughout trial completion	Descriptive statistics	>70%	10-70%	<10%
	Success of DD execution	Percentage of DD sessions successfully performed at the indicated timepoints within this setting	Data collected throughout trial completion	Descriptive statistics	>70%	10-70%	<10%

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	CURATE.AI degree of execution	Percentage of patients to whom we successfully apply CURATE.AI profile analysis to	Data collected throughout trial completion	Descriptive statistics	>70%	10-70%	<10%
	Compliance response	The percentage of patients requiring and responding to reminders to complete DI/DD sessions	Data collected throughout trial completion	Descriptive statistics	-	-	-
Practicality	DI/DD practicality	Trial team perception of the ability of patients to carry out DI/DD activities	Data collected from focus group with trial team members at end of trial	Thematic analysis	-	-	-
	Logistical feasibility	Logistical considerations with current trial protocol that would need to be addressed or accounted for a future RCT	Data collected from focus group with trial team members at end of trial	Thematic analysis	-	-	-
Limited-efficacy testing	DI limited efficacy	Exploratory analysis of the DI on the intended change in cognitive functioning pre-post intervention	Data collected from cognitive evaluation and DD sessions of the trial	Descriptive statistics	-	-	-
	DD limited efficacy	Exploratory correlational analysis of outcomes between the digital cognitive training task and standard-of-care, gold standard cognitive evaluations	Data collected from cognitive evaluation and DD sessions of the trial	Descriptive statistics	-	-	-

### *Secondary and Exploratory Outcomes*

Secondary outcomes of this trial include the usability of CURATE.AI COR-Tx platform as a DI and DD in brain tumour patients post-radiotherapy. Usability will be evaluated qualitatively as part of the semi-structured interview session.

Exploratory outcomes will include the user experience (UX) of the CURATE.AI COR-Tx platform as a DI and DD in brain tumour patients post-radiotherapy. UX will be evaluated qualitatively in the semi-structured interview session. Further, as the participants will use the CURATE.AI COR-Tx platform throughout the duration of their care, it is possible that the objective, quantifiable physiological and behavioural data collected from the DTx, known as digital biomarkers, may offer the ability to detect changes in cognitive function and declines in these patients [33]. Therefore, an additional exploratory outcome will include capturing and preliminary evaluation of potential digital biomarkers for cognitive function and declines during the DI sessions.

### *Patient-Centred Outcomes*

#### *Cognitive Function*

The non-digital cognitive evaluations will be used to assess different domains of cognitive functioning including memory, verbal fluency, executive function and global function, and serve as the “gold standard” comparison to evaluate the limited efficacy of the CURATE.AI CORTx platform as a DI and DD. All combined non-digital cognitive evaluations will be performed by a clinical neuropsychologist who will administer the test battery as recommended by the Radiotherapy Oncology Group (RTOG) [41]. Memory impairment will be assessed using the Hopkins Verbal Learning Test (HVLT) [42]. Verbal fluency will be assessed using the Controlled Oral Word Association Test

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3 (COWAT) [43]. Executive function will be assessed using the Trail Making Test (Parts  
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5 A and B) [44]. Global cognitive functioning will be assessed using the Mini-Mental  
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7 State Examination (MMSE) [45]. Patient reported health related quality of life will be  
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9 assessed using the SF-36 [46]. Skill transfer will be assessed using the Functional  
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11 Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) [47,48] and Cognitive  
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13 Failures Questionnaire [49]. Finally, the same clinical neuropsychologist will  
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15 administer DD session which will be recorded via the CURATE.AI COR-Tx platform.  
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17 Each combined non-digital cognitive evaluation and DD session will take  
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19 approximately one hour to complete and will be performed at the Department of  
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21 Radiation Oncology clinic at NCIS.  
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### 29 **Qualitative and Statistical Analysis**

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31 We will perform and report descriptive and inferential statistical analyses of the  
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33 quantitative outcome measures. For qualitative outcomes thematic analysis will be  
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35 used. All interviews and focus group sessions will be recorded and transcribed  
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37 verbatim. Coding will be done manually. The analysis will follow the three stages: (1)  
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39 data will be descriptively labelled (open coding); (2) labelled data will be grouped into  
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41 categories based on literature (secondary coding); and (3) understanding the  
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43 categories to create broader themes/assertions [50]. We will not statistically analyse  
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45 exploratory outcomes.  
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### 51 **Data Availability**

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53 Data generated and/or analysed during this clinical feasibility trial will be made  
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55 available from the corresponding author on reasonable request.  
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## Safety Monitoring and Data Storage

### Safety Monitoring

The clinically trained Principal Investigator (PI) will oversee and monitor the conduct of this study to ensure the health and safety of participants and the validity and integrity of the data. Participants will be fully informed of the study requirements throughout the conduct of the study and should comply with the research protocol or be allowed to withdraw from participation. The PI will notify participants of any information relevant to their continued participation. Specifically, the PI will review the research protocol, evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site, and other factors that can affect study outcome. Scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study will be considered. The PI will make recommendations to the Domain Specific Review Board (DSRB) and trial site concerning continuation or conclusion of the trial. The PI will protect the confidentiality of the trial data and the results of monitoring. CURATE.AI COR-Tx will only recommend the training intensity within the pre-specified intensity.

### Safety reporting and monitoring

Adverse events (AE) and serious adverse events (SAE) will be monitored and recorded. All AEs will be recorded on the patient's case report form (CRF) from date of informed consent to 30 days following the last therapy session or initiation of new therapy, whichever occurs first. All treatment-related AEs will be followed until resolution of or until initiation of new therapy, whichever occurs first. During the long-term follow-up period, only secondary malignancies will be captured as AE. For both

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3 AEs and SAEs, the investigator will provide a record of the start and stop dates of the  
4 event, the action taken with study treatment as a result of the event (e.g.,  
5 discontinuation or reduction of study treatment), and outcome of the event. In the event  
6 of a possible study treatment-related AE, the investigator will to the best of his/her  
7 ability assess its relationship to the study treatment. If an AE is considered serious,  
8 both the AE page/screen of the CRF and the SAE Report Form will be completed.  
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### 19 Data Storage

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21 Participants will interact with the CURATE.AI COR-Tx platform on trial provided  
22 tablets. Participant-identifying information (name, contact number, email) and the data  
23 linking subject identifiers and the subject identification codes will be collected and  
24 stored on one of the laboratory password-protected computers, which are kept in  
25 locked office rooms by the clinical team, separately from the research data to ensure  
26 that participants cannot be individually matched to their data. Clinical data will be  
27 stored on the Research Electronic Data Capture (REDCap) platform, a secure web  
28 application for building and managing online databases compliant with 21 Code of  
29 Federal Regulations (CFR) Part 11, Federal Information Security Management Act  
30 (FISMA), Health Insurance Portability and Accountability Act (HIPAA) and General  
31 Data Protection Regulation (GDPR), purposefully built to support online and offline  
32 data capture for research. While the study is ongoing, the de-identified (coded)  
33 research data will be retrieved from REDCap by the data analysis team and stored on  
34 one of the laboratory password-protected computers, which are kept in locked office  
35 rooms. Participants will be provided with a unique account and password to access  
36 sessions on the CURATE.AI COR-Tx platform. Only their own performance data will  
37 be stored within their unique account and on the secure cloud platform. Only the  
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3 technical team will have access to the CURATE.AI COR-Tx platform performance  
4 data. Only the PI and collaborators will have access to the de-identified trial data.  
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10 Audio recordings and transcripts (with no identifiers revealed) of the semi-structured  
11 interviews will be coded and stripped of identifying information at the earliest  
12 opportunity to ensure confidentiality of the participants. Participant-identifying  
13 information will be discarded upon the completion of the research. Research data will  
14 be kept for future meta-analyses (including power analyses) and other occasions when  
15 the original data need to be referenced. These data will be retained for at least 10  
16 years.  
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### 28 **Patient and Public Involvement**

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30 This feasibility clinical trial was designed without patient and public involvement.  
31 However, this feasibility clinical trial includes a mixed-methods approach including  
32 semi-structured patient participant interviews with aims to explore acceptability,  
33 usability and user experience of the CURATE.AI COR-Tx platform as a DI and DD.  
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35 The valuable input we will receive from these patient participants will be incorporated  
36 into the design of a future RCT.  
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### 47 **Ethics and dissemination**

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49 This study has been approved by the National Healthcare Group (NHG) DSRB,  
50 reference: DSRB2020/00249. Clinical investigators will explain the protocol and obtain  
51 written, informed consent from patients as per the protocol prior to taking part in the  
52 study. We will report our findings at scientific conferences and/or in peer-reviewed  
53 journals. We will not publish any personal health identifiers.  
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### Author contributions

XT, AB, TK, DC, CLA, DH and BAV developed the study concept and initiated the project. AR, XT, GNSK, AB, TK, SV, LN, MR, WTDC, CLA, DH and BAV provided significant input into the development of the protocol. AR, SV, MR, QYC, FA, TKJ, YTT, AW, WTDC and BAV will implement the protocol and oversee the collection of the data. AR and XT drafted the manuscript, and all authors (AR, XT, GNSK, AB, TK,

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3 SV, LN, MR, QYC, FA, YR, TKJ, YTT, AW, WTDC, CLA, DH and BAV) read,  
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5 contributed to and approved the final manuscript.  
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### 9 **Competing interests**

10  
11 AB, TK, CLA and DH are co-inventors of previously filed pending patents on artificial  
12  
13 intelligence-based therapy development. DH and TK are shareholders of KYAN  
14  
15 Therapeutics, which has licensed intellectual property pertaining to AI-based  
16  
17 oncology drug development and personalised medicine.  
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26  
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### Figure Legends

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32 **Figure 1.** CURATE.AI COR-Tx platform digital cognitive training tasks  
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34 **Figure 2.** Feasibility SPIRIT trial schedule and investigations  
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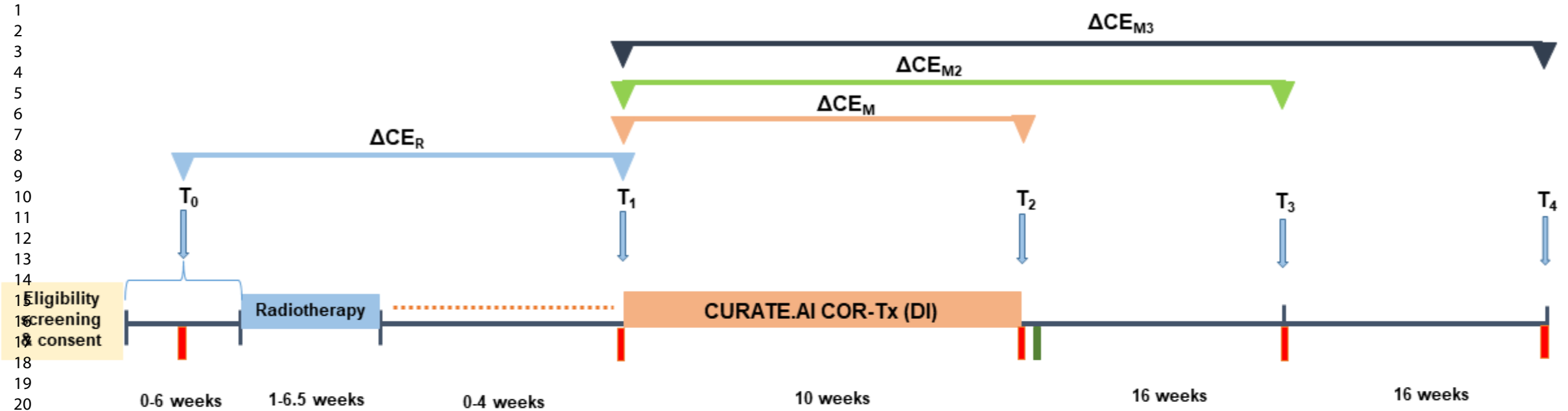
Modified Multi-Attribute Task Battery (MATB-M)



Perceptual Learning Task (PLT)



Updating Memory Task (UMT)



- 24 CURATE.AI COR-Tx platform (DI): CURATE.AI COR-Tx platform as a digital intervention (session intensity guided by CURATE.AI for each patient using their own data)
- 25 CURATE.AI COR-Tx Platform (DD): CURATE.AI COR-Tx platform as a digital diagnostic (session intensity is a fixed sequence for all patients)
- 26 Post-CURATE.AI COR-Tx platform (DI) semi-structured interview
- 27  Variable time to start CURATE.AI COR-Tx platform (DI) post radiotherapy dependent on patient's recovery and follow-up clinical appointment
- 28  $T_0$ : Pre-radiotherapy cognitive evaluation
- 29  $T_1$ : Post-radiotherapy cognitive evaluation and DD session; baseline of the CURATE.AI COR-Tx (DI)
- 30  $\Delta CE_R = T_1 - T_0$ : Effect of radiotherapy on cognitive function
- 31  $T_2$ : Post-CURATE.AI COR-Tx platform DI cognitive evaluation and DD session
- 32  $\Delta CE_M = T_2 - T_1$ : Effect of CURATE.AI COR-Tx platform (DI) on cognitive performance
- 33  $T_3$ : Post-CURATE.AI COR-Tx platform DI cognitive evaluation and DD session
- 34  $\Delta CE_{M2} = T_3 - T_1$ : Effect of CURATE.AI COR-Tx platform (DI) on cognitive performance retention
- 35  $T_4$ : Post-CURATE.AI COR-Tx platform DI cognitive evaluation and DD session
- 36  $\Delta CE_{M3} = T_4 - T_1$ : Effect of CURATE.AI COR-Tx platform (DI) on cognitive performance retention

Essential:  $T_1, T_2$   
 Desirable:  $T_0, T_3$ ;  
 Optional:  $T_4$

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Doc Name : Informed Consent Form Template	
Doc Number : 207-001	
Doc Version : 12	Date : 30 Nov 2018

## INFORMED CONSENT FORM

### 1. Study Information

#### Protocol Title:

An N-of-1 pilot study of CURATE.AI to optimise cognitive training in post-brain radiotherapy patients

#### Principal Investigator & Contact Details:

Dr. Bala Vellayappan  
Consultant, Department of Radiation Oncology  
National University Cancer Institute Singapore (NCIS)  
Tel:+65 6779 5555

#### Study Sponsor:

Singapore Cancer Society.

### 2. Purpose of the Research Study

You are invited to participate in a research study. It is important to us that you first take time to read through and understand the information provided in this sheet. Nevertheless, before you take part the study will be explained to you and you will be given the chance to ask questions. After you are satisfied that you understand this study, and that you wish to take part in the study, you must sign this informed consent form. You will be given a copy of this consent form to take home with you.

You are invited because you have been diagnosed with a brain tumour and you are being planned to be treated with radiotherapy. Patients treated with radiotherapy directed to the brain may experience cognitive decline post-treatment. There are drug-based approaches to counteract the unwanted effects of radiotherapy, but these are usually limited in efficacy. Alternatively, patients can be treated with digital therapy, which seeks to improve patient's cognitive performance. Digital therapeutics are a new category of apps that help prevent or treat diseases by modifying patient behavior and/or providing remote monitoring to improve long-term health outcomes. However, most digital therapies are administered at fixed intensity, without accounting for differences between patients. This study is carried out to find out whether personalised (as opposed to fixed) intensity training in a digital therapeutic platform can improve cognitive performance. To that end, an artificial intelligence platform called CURATE.AI will be used to dynamically vary the intensity of a digital cognitive test battery.

This study aims to recruit 15 participants over a period of two years. The subjects would be recruited from National University Hospital.

### 3. What procedures will be followed in this study

If you take part in this study, you will be asked to complete cognitive evaluation and quality of life questionnaires. Among other things, you will have to recall words that were read to you, do mathematical calculations, connect numbers in a certain order, and self-assess your health. You will also perform some cognitive tasks on a tablet. The digital cognitive test battery will consist of three tasks: the number memory task, the Gabor Patch perceptual

1 learning task and the MATB (Multi-Attribute Task Battery) task. In the number memory task,  
2 you will be asked to recall the last presented items (e.g. the last 4 numbers) from a list of  
3 continuously updated items. In the Gabor patches task, you will be asked to discriminate  
4 between two briefly presented patches, indicating which direction the patches rotated  
5 (clockwise or counterclockwise). In the MATB task, you will be asked to virtually turn lights on  
6 and off, track elements on the screen, keep a cursor in a certain place or virtually control the  
7 flux of liquid between tanks. Depending on the case, you might do all or some of the tasks.

8  
9 Your participation in the study will last one year, during which you will use the digital  
10 cognitive intervention 35 times and visit the doctor's office 5 times.

11  
12 If you agree to take part in this study, the following will happen to you:

13  
14  
15 **Visit 1 (pre-radiotherapy):** During your first visit, before radiotherapy starts, your baseline  
16 data will be collected, and you will complete a cognitive evaluation and a 10-15 minute  
17 cognitive training session.

18  
19 **Visit 2 (pre-intervention):** after radiotherapy completion, and right before cognitive training,  
20 you will complete a cognitive evaluation and a 10-15 minute cognitive training session.

21  
22 **Visit 3 (post-intervention):** you will complete a cognitive evaluation and a 10-15 minute  
23 cognitive training session.

24  
25 **Interview visit (post-intervention):** you will complete a 60 minute semi-structured interview  
26 about your experience with the intervention. Ideally, this will happen at visit 3, but may occur  
27 up to 5 days after depending on your schedule. The questions will cover your experience  
28 performing the tasks of the interface. If you do decide to participate and later wish to  
29 withdraw you may do so as well. You do not have to answer any question you do not wish to.  
30 The interview will be audio taped and transcribed for purposes of data analysis. Your data  
31 will be confidential and will be used solely for research to improve the interface/intervention.  
32 The interviews can happen via video chat or in any place convenient to you and any day  
33 around the date you are doing the cognitive evaluation, also at your convenience. Audio  
34 recordings and transcripts will not reveal identifiers and will be coded (stripped of identifying  
35 information) at the earliest opportunity.

36  
37 **Visit 4 (16 weeks post-intervention):** you will complete a cognitive evaluation and a 10-15  
38 minute cognitive training session.

39  
40 **Visit 5 (32 weeks post-intervention):** you will complete a cognitive evaluation and a 10-15  
41 minute cognitive training session.

42  
43 When your participation in the study ends, you will no longer have access to the cognitive  
44 test battery/CURATE.AI, unless special arrangements are made by the Principal Investigator.

45  
46 Any individually-identifiable data obtained during the course of this study will be stored for the  
47 purposes of this study only and will not be used for future biomedical research. De-identified  
48 data will be kept for future studies only with your consent and only for the purpose you  
49 consent (either general research or research related to brain cancer).

50  
51 Your personal information (name, contact number, email) and the document linking your  
52 information to your identification code will be collected and stored separately from the  
53 research data to ensure that you cannot be individually matched to your data. Personal data  
54 will be discarded upon completion of the study. De-identified data will be stored for a period  
55 of ten years on a password-protected computer kept in a locked office room. Only the PI and  
56 collaborators will have access to the data.

57  
58 During the course of the study, there is a possibility that we might unintentionally come to  
59 know of new information about your health condition from the tests that are conducted as  
60

part of the study. These are called “incidental findings”. You will be asked to indicate whether you wish to be re-identified and notified in the case of a clinically significant incidental finding that is related to you.

#### 4. Your Responsibilities in This Study

If you agree to participate in this study, you should follow the advice given to you by the study team. You should be prepared to visit the hospital 5 times and undergo all the procedures that are outlined above.

#### 5. What Is Not Standard Care or is Experimental in This Study

The study is being conducted because the CURATE.AI-modulated digital cognitive test battery is not yet proven to be a standard treatment in subjects with brain tumour undergoing radiotherapy. We aim to study CURATE.AI-modulated digital cognitive test battery as a potential treatment for your condition.

#### 6. Possible Risks and Side Effects

No anticipated risks or side effects are expected from subjects’ participation in the study.

#### 7. Possible Benefits from Participating in the Study

There is no assurance you will benefit from participation in this study, but you may experience improved cognitive performance. Additionally, your participation in this study will add to the medical knowledge about the use of this intervention.

#### 8. Alternatives to Participation

If you choose not to take part in this study, you will continue to receive the standard care for your condition. The benefits are, for primary brain tumour patients, improved tumour control; for brain metastasis patients, relief of symptoms.

Your decision not to participate in this study will in no way affect your continued care in this institution with your physician.

#### 9. Costs & Payments if Participating in the Study

If you take part in this study, the following will be performed at no charge to you: digital cognitive training and cognitive evaluations. These costs will be borne by the Singapore Cancer Society.

If you take part in this study, you will have to pay for the following: standard care including diagnostic scans and radiotherapy treatment.

Only if you complete the study you will be compensated for the participation time with the computer tablet used for your digital therapy.

#### 11. Voluntary Participation

Your participation in this study is voluntary. You may stop participating in this study at any time. Your decision not to take part in this study or to stop your participation will not affect

1 your medical care or any benefits to which you are entitled. If you decide to stop taking part  
2 in this study, you should tell the Principal Investigator.  
3

4 However, the data that has been collected until the time of your withdrawal will be kept and  
5 analysed.  
6

7  
8 Your doctor, the Investigator and/or the Sponsor of this study may stop your participation in  
9 the study at any time if they decide that it is in your best interest. They may also do this if you  
10 do not follow instructions required to complete the study. If you have other medical problems  
11 or side effects, the doctor and/or nurse will decide if you can continue in the research study.  
12

13 In the event of any new information becoming available that may be relevant to your  
14 willingness to continue in this study, you (*or your legally acceptable representative, if*  
15 *relevant*) will be informed in a timely manner by the Principal Investigator or his/her  
16 representative.  
17

## 18 **12. Compensation for Injury**

19  
20  
21 If you follow the directions of the doctors in charge of this study and you are physically  
22 injured due to the trial substance or procedure given under the plan for this study, National  
23 University Hospital will pay the medical expenses for the treatment of that injury.  
24

25 Payment for management of the normally expected consequences of your treatment will not  
26 be provided by National University Hospital.

27 National University Hospital without legal commitment will compensate you for the injuries  
28 arising from your participation in the study without you having to prove National University  
29 Hospital is at fault. There are however conditions and limitations to the extent of  
30 compensation provided. You may wish to discuss this with your Principal Investigator.  
31

32 By signing this consent form, you will not waive any of your legal rights or release the parties  
33 involved in this study from liability for negligence.  
34

## 35 **13. Confidentiality of Study and Medical Records**

36  
37  
38 Your participation in this study will involve the collection of "Personal Data". "Personal Data"  
39 means data about you which makes you identifiable (i) from such data or (ii) from that data  
40 and other information which an organisation has or likely to have access. This includes  
41 medical conditions, medications, investigations and treatment history.  
42

43 Information and "Personal Data" collected for this study will be kept confidential. Your  
44 records, to the extent of the applicable laws and regulations, will not be made publicly  
45 available.  
46

47 However, National University Health System, Regulatory Agencies, NHG Domain Specific  
48 Review Board and Ministry of Health will be granted direct access to your original medical  
49 records to check study procedures and data, without making any of your information public.  
50 By signing the Informed Consent Form attached, you (*or your legally acceptable*  
51 *representative, if relevant*) are authorising (i) the collection, access to, use and storage of  
52 your "Personal Data", and (ii) the disclosure to authorised service providers and relevant third  
53 parties.  
54

55 Data collected and entered into the Case Report Forms are the property of NCIS. In the  
56 event of any publication regarding this study, your identity will remain confidential.

57 Research arising in the future, based on your "Personal Data", will be subject to review by  
58 the relevant institutional review board.  
59  
60



1  
2 Any information containing your "Personal Data" that is collected for the purposes described  
3 in this Informed Consent Form will not be transferred out of Singapore.

4 By participating in this research study, you are confirming that you have read, understood  
5 and consent to the Personal Data Protection Notification available at  
6 <https://www.nuh.com.sg/Pages/Personal-Data-Protection-Act.aspx>.  
7  
8  
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#### 10 **14. Conflict of Interest Disclosure**

11  
12 1) Prof Ho is a co-inventor of *Phenotypic Personalised Medicine: Adaptive Optimization of*  
13 *Patient-Specific Combination Therapy*; The current study uses the same core technology but  
14 for a different functionality and it is unlikely to be affected by this conflict of interest.

15  
16 2) Prof Ho is a co-inventor of *Nanomedicine Optimization with Feedback System Control and*  
17 *Cognitive Training Platform, which outlined the usage of CURATE.AI*. The current study  
18 relates to this inventions by using the same core technology and therefore it may be affected  
19 by this conflict of interest.  
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21  
22 3) Prof Ho is a co-inventor of *Multi-Drug Therapies for Tuberculosis Treatment and Novel*  
23 *Optimised Drug Combinations for Drug-Resistant and Drug-Sensitive Multiple Myeloma*  
24 *Developed Using A Systematic Phenotypic Personalised Medicine*. These inventions do not  
25 relate to the same technology as the current study and hence this conflict of interest does not  
26 affect the current study.  
27

28 4) Prof Dean Ho is a co-founder and shareholder in KYAN Therapeutics. KYAN Therapeutics  
29 is in the process of finalizing licensing agreement for some of the technology platforms listed  
30 above, that may be used for this study and therefore it may be affected by this conflict of  
31 interest.  
32

33 1) Dr Blasiak is a co-inventor of *Cognitive Training Platform, which outlined the usage of*  
34 *CURATE.AI*. The current study relates to this inventions by using the same core technology  
35 and therefore it may be affected by this conflict of interest.  
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#### 41 **15. Who To Contact if You Have Questions**

42  
43 If you have questions about this research study, you may contact the Principal Investigator,

44  
45 Dr. Bala Vellayappan  
46 Consultant, Department of Radiation Oncology  
47 National University Cancer Institute Singapore (NCIS)

48  
49 Tel:+65 6779 5555

50 The study has been reviewed by the NHG Domain Specific Review Board (the central ethics  
51 committee) for ethics approval.

52  
53 If you want an independent opinion to discuss problems and questions, obtain information  
54 and offer inputs on your rights as a research subject, you may contact the NHG Domain  
55 Specific Review Board Secretariat at 6471-3266. You can also find more information about  
56 participating in clinical research, the NHG Domain Specific Review Board and its review  
57 processes at [www.research.nhg.com.sg](http://www.research.nhg.com.sg).  
58

59 If you have any complaints or feedback about this research study, you may contact the  
60

1 Principal Investigator or the NHG Domain Specific Review Board Secretariat.  
2  
3

4 **16. Consent to be Contacted for Future Research**  
5  
6

7 You are being asked for permission to be contacted in the future for participation in research  
8 studies that you may be suitable for. If you agree to be contacted, your information and  
9 contact details will be entered and stored in a secured database in NCIS. Your information  
10 and contact details will not be released to any parties outside NCIS without your permission.  
11 When investigators from NCIS identify you to be suitable for a particular research study, the  
12 investigators or authorised personnel from NCIS will contact you to inform you about the  
13 research study. Your decision to be contacted for future research studies is completely  
14 voluntary and separate from your decision to participate in this study. Your decision will not  
15 affect your medical care or any benefits to which you are entitled. You may change your  
16 mind at any time by contacting the principal investigator.  
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## CONSENT FORM

### Protocol Title:

An N-of-1 pilot study of CURATE.AI to optimise cognitive training in post-brain radiotherapy patients

### Principal Investigator & Contact Details:

Dr. Bala Vellayappan  
Consultant, Department of Radiation Oncology  
National University Cancer Institute Singapore (NCIS)  
Tel:+65 6779 5555

I voluntarily consent to take part in this research study. I have fully discussed and understood the purpose and procedures of this study. This study has been explained to me in a language that I understand. I have been given enough time to ask any questions that I have about the study, and all my questions have been answered to my satisfaction. I have also been informed and understood the alternative treatments or procedures available and their possible benefits and risks.

By participating in this research study, I confirm that I have read, understood and consent to the National University Hospital Personal Data Protection Notification

### Consent for the Participation in Volunteer Interviews

- Yes, I agree to participate in the voluntary interviews.
- No, I do not agree to participate in the voluntary interviews

### Consent for the Use of Data for Future Research

- Yes, I agree to donate my data for future research.

*Please also check one of these boxes:*

- There are no restrictions on the kind of research that may be done with my data.
- The Investigator may use my data for future research as long as the research is related to brain cancer.
- No, I do not agree to donate my data for future research.

### Consent to be Re-Identified and Notified in the Case of an Incidental Finding

- Yes, I agree to be re-identified and notified in the case of an incidental finding from this research.

In the event that I cannot be reached, please contact my next of kin

Name of next of kin:

Contact:

No, I do not agree to be re-identified and notified in the case of an incidental finding from this research.

**Consent to be Contacted for Future Research**

Yes, I agree to be for contacted for future research that I may be eligible for.  
I agree to be contacted via:

Phone \_\_\_\_\_

Mail \_\_\_\_\_

Email \_\_\_\_\_

Others \_\_\_\_\_

No, I do not agree to be contacted for future research.

\_\_\_\_\_  
Name of Participant

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

**Witness Statement**

I, the undersigned, certify that:

- I am 21 years of age or older.
- To the best of my knowledge, the participant/ the participant's legally acceptable representative signing this informed consent form has the study fully explained in a language understood by him/ her and clearly understands the nature, risks and benefits of his/ her participation in the study.
- I have taken reasonable steps to ascertain the identity of the participant/ the participant's legally acceptable representative giving the consent.
- I have taken steps to ascertain that the consent has been given voluntarily without any coercion or intimidation.

\_\_\_\_\_  
Name of Witness

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

1. In accordance with Section 6(d) of the Human Biomedical Research Act and Regulation 25 of the Human Biomedical Research Regulations 2017, appropriate consent must be obtained in the presence of a prescribed witness who is 21 years of age or older, and has mental capacity. The witness must be present during the entire informed consent discussion, and must not be the same person taking the appropriate consent. The witness may be a member of the team carrying out the research.
2. However, if the participant/ the participant's legally acceptable representative is unable to read, and/ or sign and date on the consent form, an impartial witness should be present instead. The impartial witness should not be a member of the study team.

**Investigator Statement**

I, the undersigned, certify that I explained the study to the participant and to the best of my knowledge the participant signing this informed consent form clearly understands the nature, risks and benefits of his / her participation in the study.

Name of Investigator / Person administering consent	Signature	Date
--------------------------------------------------------	-----------	------

For peer review only

## Voluntary Interview Guide

### Demographic Details

- Age
- Gender
- Education
- Occupation
- Clinical status

### Theme 1: Project objective (Why the choice?)

- Could you tell us why you decided to participate in the study?
- What are you trying to achieve/what are your expectations?
- What are some alternatives you may try instead of this? And why?
- What do you feel about the interface/intervention?
- What were you looking for when you were informed of such a project?
- What do you feel about the instructions?
- Could you comment on this method of training/evaluation?
- Do you think it's appropriate to be randomised into a control group in a future clinical trial?

### Theme 2: Overall experience (What facilitates and what hinders?)

- What do you like about the interface/intervention?
- What don't you like?
- Is there something you've done previously that's similar?
- Would you know anyone who might enjoy this interface?- Could you describe those people?
- What is your opinion on the time taken- Overall, task wise?
- What are your thoughts about the doctor's absence in this?
- How confident do you feel using the interface?
- Did you face difficulties? Could you elaborate?
- What was easy in do in this?
- What is good about this? What isn't?
- Would you voluntarily do it?
- Is this something you would like as part of your formal treatment?
- How would you like to use it- the medium, ideas on the interface?
- Do you think there were or there could be any adverse events in this?

### Theme 3: Training (How do you help people to use the interface?)

- What did you learn?
- How did it help?
- What could have been better?
- How was the explanation/instructions?



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Abstract/Title Page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract/Title Page/Methods/Analyses
	2b	All items from the World Health Organization Trial Registration Data Set	_____ NA _____
Protocol version	3	Date and version identifier	_____ NA _____
Funding	4	Sources and types of financial, material, and other support	Funding Statement
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page/Author contribution statement
	5b	Name and contact information for the trial sponsor	_____ NA _____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Funding Statement

1 5d Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint  
 2 adjudication committee, data management team, and other individuals or groups overseeing the trial, if  
 3 applicable (see Item 21a for data monitoring committee) \_\_\_\_\_NA\_\_\_\_\_

## 9 Introduction

10  
 11 Background and 6a Description of research question and justification for undertaking the trial, including summary of Introduction  
 12 rationale relevant studies (published and unpublished) examining benefits and harms for each intervention  
 13  
 14 6b Explanation for choice of comparators Introduction  
 15  
 16 Objectives 7 Specific objectives or hypotheses Introduction  
 17  
 18 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), Trial Design  
 19 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)  
 20  
 21

## 22 Methods: Participants, interventions, and outcomes

23  
 24 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data Trial Design  
 25 will be collected. Reference to where list of study sites can be obtained  
 26  
 27 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and Study Setting and  
 28 individuals who will perform the interventions (eg, surgeons, psychotherapists) Participants  
 29  
 30 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will Intervention  
 31 be administered  
 32  
 33 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose Safety Monitoring  
 34 change in response to harms, participant request, or improving/worsening disease)  
 35  
 36 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring CURATE.AI COR-Tx  
 37 adherence (eg, drug tablet return, laboratory tests) Platform Digital  
 38 Intervention (DI)  
 39  
 40  
 41  
 42

1		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____NA_____
2	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Outcomes
3				
4				
5	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Trial Schedule and Investigations
6				
7	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Sample Size
8				
9	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____NA_____
10				
11	<b>Methods: Assignment of interventions (for controlled trials)</b>			
12	Allocation:			
13	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____NA_____
14				
15				
16	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____NA_____
17				
18	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____NA_____
19				
20	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____NA_____
21				
22		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____NA_____
23				
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1 **Methods: Data collection, management, and analysis**

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3 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related Outcomes

4 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a

5 description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and

6 validity, if known. Reference to where data collection forms can be found, if not in the protocol

7

8

9 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be \_\_\_\_\_ - \_\_\_\_\_

10 collected for participants who discontinue or deviate from intervention protocols

11

12 Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote data Data Management

13 quality (eg, double data entry; range checks for data values). Reference to where details of data

14 management procedures can be found, if not in the protocol

15

16

17 Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of Qualitative and

18 the statistical analysis plan can be found, if not in the protocol Statistical Analysis/

19 Table 1

20

21 20b Methods for any additional analyses (eg, subgroup and adjusted analyses) \_\_\_\_\_NA\_\_\_\_\_

22

23 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and

24 any statistical methods to handle missing data (eg, multiple imputation) \_\_\_\_\_NA\_\_\_\_\_

25

26

27 **Methods: Monitoring**

28

29 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; \_\_\_\_\_NA\_\_\_\_\_

30 statement of whether it is independent from the sponsor and competing interests; and reference to

31 where further details about its charter can be found, if not in the protocol. Alternatively, an explanation

32 of why a DMC is not needed

33

34

35 21b Description of any interim analyses and stopping guidelines, including who will have access to these Safety Monitoring

36 interim results and make the final decision to terminate the trial

37

38 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse Safety Monitoring

39 events and other unintended effects of trial interventions or trial conduct

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1	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____NA_____
2				
3				
4	<b>Ethics and dissemination</b>			
5				
6	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Ethics and dissemination
7				
8				
9	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____ - _____
10				
11				
12				
13				
14	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Consent Procedure
15				
16				
17		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Consent Procedure
18				
19				
20	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Data Management
21				
22				
23	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Declarations of Interest
24				
25				
26				
27	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Data management
28				
29				
30	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____NA_____
31				
32				
33	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____22_____
34				
35				
36				
37				
38		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ - _____
39				
40		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ - _____
41				
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1 **Appendices**

2

3 Informed consent 32 Model consent form and other related documentation given to participants and authorised surrogates \_\_\_\_\_Supplemental

4 materials file 1\_\_\_\_\_

5

6 Biological 33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular \_\_\_\_\_ - \_\_\_\_\_

7 specimens analysis in the current trial and for future use in ancillary studies, if applicable

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10 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.

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