BEACON TRIAL PROTOCOL & STATISTICAL ANALYSIS PLAN

Full study title: Online brain training for people with cognitive impairment following SARS-CoV-2 infection: A randomised controlled clinical trial.

Short study title: Brain Training App for Cognition in People with Long Covid (BEACON)

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Chief Investigator	Professor Anne Corbett

This protocol has regard for the HRA guidance and order of content

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Sponsor:

Signature:		Date:	XX / XX / 2023
Name (please print): \	Dr Antony Walsh		
Position:	Head of Research Governance, Ethics and Compliance		
Signature:		Date:	01 / September / 2025
Name:	Prof. Anne Corbett		
Position	Professor of Dementia Research, PROTECT Study Lead & BEACON Trial Chief Investigator		

This protocol describes the BEACON trial and provides information about procedures for participants taking part in the BEACON trial. The protocol should not be used as a guide for treatment of patients not taking part in the BEACON trial.

AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
2022-23-22 SA 1	*03 October 2023*	*2.0*	*Substantial Amendment No. 1*	- *Deletion of reference to informant or study partner* - *-Change in sponsor contact details* - *Clarify site type for PIC activities*
2022-23-22 SA 2	*09 January 2024*	*3.0*	*Substantial Amendment No. 2*	- *Update to description of the FLAME cognitive test system to ensure it aligns with software update.* - *Addition of information on DNA sample collection requirement.* - *Addition of information to clarify that interested pharmacies, care homes, gyms, dental clinics, eye clinics etc can advertise the BEACON study using the approved study poster.*
N/A	*01 September 2025*	*4.0*	*N/A*	- *Increase of age for primary analysis population from over 40 to over 50 based on baseline data suggesting discrimination between Long Covid and Healthy increases substantially beyond age 50.* - *Removal of six week as a co-primary based on low completion rates at six week assessments*

				and low training completion in the first six weeks of the trial - *Including Statistical Analysis Plan as an Appendix*

ABBREVIATIONS

AE	Adverse event
CI	Chief Investigator
COVID-19	Coronavirus Disease 19
COSMO	Cognition Online Sleep Monitoring Scale
CSRI	Client Service Receipt Inventory
DMEC	Data Monitoring & Ethics Committee
FACIT	Functional Assessment of Chronic Illness Therapy – Fatigue
FDA	U.S. Food and Drug Administration
GAD-7	Generalised Anxiety Disorder
GCP	Good Clinical Practice
ICF	Informed Consent Form
IADL	Instrumental Activities of Daily Living
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
ISRCTN	International Standard Randomised Controlled Trials Number
NHS R&D	National Health Service Research & Development
PASC	Post-acute Sequelae of SARS-CoV-2 Infection
PCFS	Post-COVID-19 Functional Status
PHQ-9	Patient Health Questionnaire
PI	Principal Investigator
PII	Participant Identifiable Information
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PROTECT	Platform for Research Online to Investigate Genetics and Cognition and Ageing
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Control Trial
REC	Research Ethics Committee
ReaCT	Reasoning Cognitive Training
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
WG-SS	Washington Group Short Set on Functioning

SCHEDULE OF EVENTS

Events (BEACON)	Screening		Assessment		
			Day 1 (+/7 days)	Week 6 (+/7 days)	Week 26 (+/7 days)
Eligibility Assessment	X	ENROLMENT			
Informed consent	X[a]				
FLAME Battery			X[b]	X	X
Brain Training Games (ReaCT or Control)[c]			X	X	X
Subjective Cognitive Decline Questionnaire			X	X	X
Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE, Self - reported)			X	X	X
Generalised Anxiety Disorder (GAD-7)			X	X	X
Patient Health Questionnaire (PHQ-9)			X	X	X
Instrumental Activities of Daily Living (Modified six -item IADL)			X	X	X
Washington Group Short Set on Functioning (WG-SS)			X	X	X
Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT)			X	X	X
Cognitron Online Sleep Monitoring Scale (COSMOS)			X	X	X
Post-COVID Functional Status (PCFS) Scale			X	X	X
EQ-5D			X	X	X
Client Service Receipt Inventory (CSRI)			X	X	X
Adverse events reporting			X	X	X
Optional DNA (saliva) sample				X	
End of Study feedback questionnaire					X

[a] Electronic informed consent required prior to performing any trial-specific procedure; this will be required for both the participant and nominated study partner.

[b] To be completed in duplicate at baseline within 7 days of enrolment; Participant will have 12 hours to complete activity once started.

[c] The brain training games will be available at all times during the study; participates will be asked to log in and play the games for 10 minutes three times a week until the end of the study.

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FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
National Institute for Health & Care Research, Research for Patient Benefit Funding Stream	**£355,400.00**

ROLE OF TRIAL SPONSOR AND FUNDER

The study sponsor will ensure that the research team has access to resources and support to deliver the research as proposed and that responsibilities for management, monitoring and reporting of the research are in place prior to the study commencing. The sponsor will ensure that there is agreement on recording, reporting and reviewing significant developments as the research proceeds and approve any modifications to design, obtaining requisite regulatory authority approval. The sponsor will assume responsibility for operating the management and monitoring systems of the research.

Prior to the study commencing the sponsor will be satisfied that:

- The research will respect the dignity, rights, safety and well-being of participants and the relationship with healthcare professionals.
- Where appropriate the research has been reviewed and approved by an NHS Research Ethics Committee and/or the Health Research Authority Approval Programme.
- The Chief Investigator, and other key researchers have the requisite expertise and have access needed to conduct the research successfully.
- The arrangements and resources proposed for the research will allow the collection of high quality, accurate data and the systems and resources will allow appropriate data analysis and data protection.
- Organisations and individuals involved in the research agree the division of responsibilities between them.
- Arrangements are in place for the sponsor and other stakeholder organisations to be alerted to significant developments during the study, whether in relation to the safety of individuals or scientific direction.
- There are arrangements for the conclusion of the study including appropriate plans for the dissemination of findings.

The sponsor plays no role in the design of this study and will have no role in data analysis or interpretation or writing up of findings of the study.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEE

- *Trial Management Group*

The Trial Management Group will meet at least six-monthly by video conferencing. Membership will consist of the trial investigators and the trial manager.

- *Trial Steering Group / Data Monitoring and Ethics Committee*

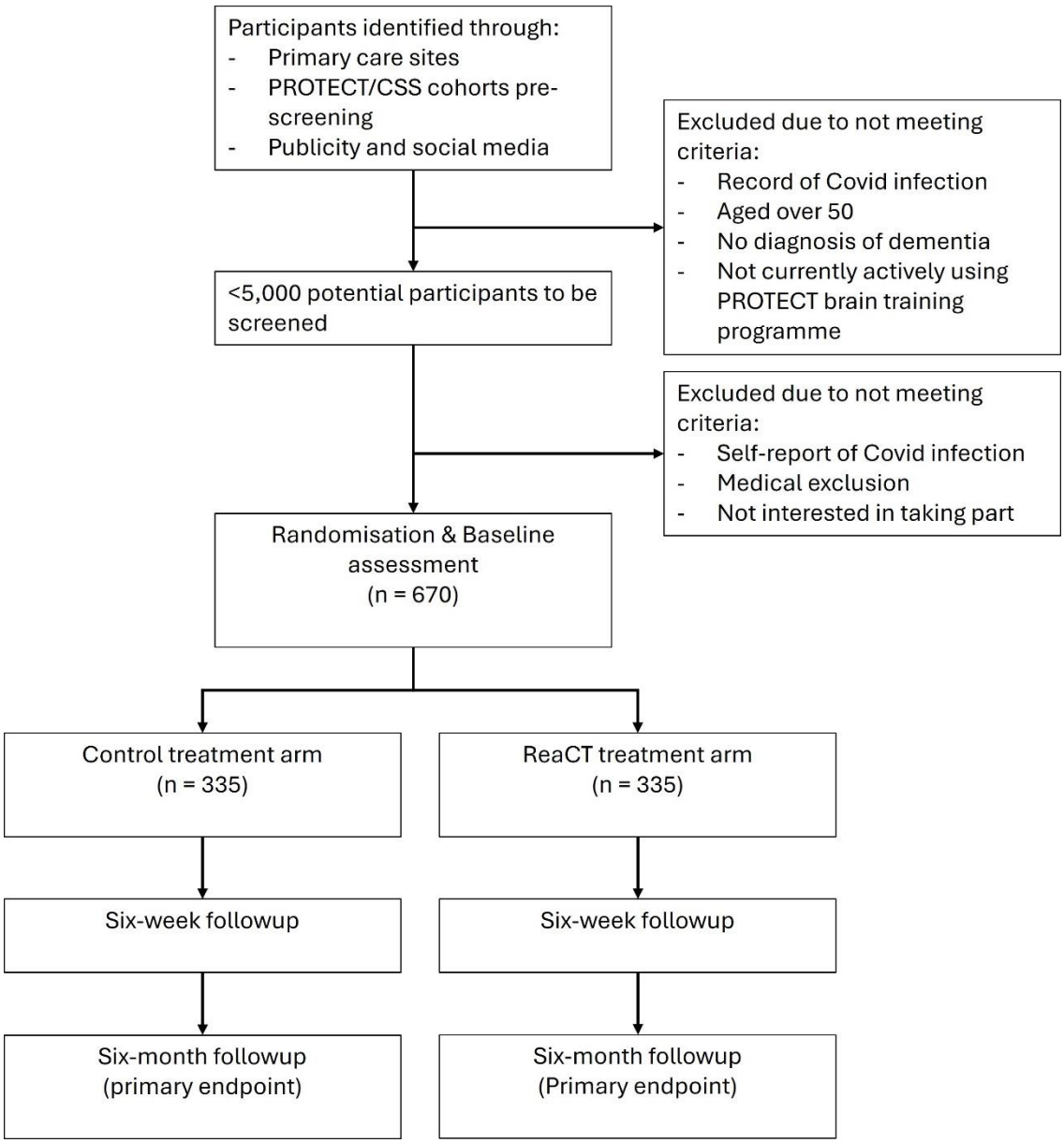
A joint TSC/DMEC will oversee the trial. This committee will meet at least six-monthly during the trial period. The trial members will include four independent members (one statistician, one lay member, two clinical advisors) and will be chaired by one of these members. The committee will also include the Chief Investigator and trial manager, with additional members of the TMG joining where required. Meetings will be split between an open session with all members, followed by a closed session for independent members only. The TSC/DMEC will have authority to end the trial early and will review any adverse events.

KEY WORDS

Cognitive Training, Online, Cognition, Long Covid, RCT

CONSORT CHART

The CONSORT chart below shows the proposed flow of participants through this study.



*CSS: COVID Symptom Study

1. BACKGROUND

The COVID-19 pandemic has had an unprecedented impact on global health, healthcare provision and society. Vaccination and improved treatment regimens are beginning to address the incidence of infections and mortality, bringing the hope that the disease will lose pandemic status and will eventually become part of the tapestry of respiratory infections in general circulation. However, there is a rapidly growing body of evidence regarding the longer-term impacts of SARS-CoV-2 infection[1,2]. The precise aetiology of Long-COVID, now referred to as post-acute sequelae of SARS-CoV-2 infection (PASC) remains to be defined, with patients reporting a wide range of protracted symptoms, including fatigue, anosmia and respiratory complaints as well as pulmonary, cardiovascular and neuropsychiatric symptoms[3-5].

There is increasing evidence for the neurological manifestations of PASC. A recent systematic review reported 66 studies, including over 250,000 patients, that examined psychiatric or neuropsychiatric sequelae in COVID-19 patients. Cognitive deficits were reported in twenty-seven of these[6], with eleven studies reported deficits affecting 25% of their cohorts, assessed up to seven months post-recovery. Impairments appear to impact across the cognitive domain spectrum including working memory, episodic memory, attention, and language. A more non-specific symptom of 'brain fog', affecting 81% of non-hospitalised patients, has also been described in the literature[7]. Further studies also report cognitive impairment following hospitalisation in 31% of patients[8]. While longer-term follow-up and epidemiological work is ongoing, the existing evidence-base clearly demonstrates the link between PASC and cognitive impairment, even in non-hospitalised patients. Cognitive impairment is a major public health issue, predominantly due to its association with increased risk for development of clinically significant cognitive decline and dementia in later life[9]. The consequences of impairments in people across younger age groups where cognitive deficit is rarer are as yet unknown, but it has the potential to cause significant concerns for individuals and place further burden on primary and secondary care settings to address this additional volume of patients. There is therefore an urgent need to address this key symptom of PASC. Given the national and global scale of the issue, it is imperative that any intervention be affordable, widely accessible, and easily administered by health professionals. Cognitive training has proven effectiveness in maintaining cognition in older adults, and can be delivered online, thus addressing the need for scalability and affordability[10].

There is good evidence to support the value of cognitive training in maintaining cognitive function and preventing progressive cognitive decline[10-15]. The landmark ACTIVE trial of in-person CT demonstrated significant and sustainable benefits in cognition and to instrumental activities of daily living, reporting a 0.25 effect size[11,16]. This magnitude of benefit, if generalisable to overall cognitive performance, would be particularly valuable at a population level. This would rely on delivery through a model involving modest cost and broad reach, which makes computerised CT particularly suitable. Our Reasoning Cognitive Training (ReaCT) computerised CT intervention builds on the ACTIVE study and achieves a further step change, demonstrating that similar levels of benefit can be achieved with an online computerized cognitive training intervention. ReaCT has been evaluated in the largest RCT of a cognitive training intervention in 6,742 individuals over the age of 50 which showed significant benefit

to reasoning, other aspects of cognition and instrumental activities of daily living in the people using ReaCT in comparison to those using a control task over six months[17].

There is increasing interest in the value of precision medicine in preventative and risk reduction approaches, including for cognitive health. A potential target factor for personalisation is genetic risk, particularly since certain genotypes or polygenic risk scores may dictate response to interventions. Remote DNA sampling techniques using non-invasive saliva sampling are now well established and can be used to conduct large-scale sampling. This approach can be used to determine any genetic component to treatment response in trials of risk reduction interventions such as cognitive training. This is particularly novel in the context of PASC since relatively little is known about the genetic determinants of Covid-related long-term health effects.

1.1 Rationale

There is a clear opportunity to evaluate the ReaCT programme as an intervention for people with PASC who are experiencing cognitive impairment. The intervention is well-established in older adults but has not been measured in this patient group. A large-scale RCT will establish effectiveness using outcomes that are specific to PASC and the COVID-19 context and will enable collection of information on the impact of the intervention on daily function, employment and health service utilisation in this group to enable a health economics evaluation. A sub-group will be sampled for genetic data to support analysis of any genetic predictor of treatment response.

1.2 Assessment and management of risk

This trial is testing the ReaCT brain training programme as an intervention accessed through a smartphone app or website. As per MHRA guidance, the intervention is not a medicinal product and thus this trial is not classified as a CTIMP.

2. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

The aim of this study is to conduct a two-arm double-blind randomised controlled trial of the ReaCT cognitive training programme in adults with subjective or established cognitive impairment following infection with SARS-CoV-2 with a view to a future roll-out of the programme on a population-wide basis.

2.1 Primary Research Question

What is the impact of the ReaCT programme on executive function as measured using the verbal reasoning task (part of the FLAME cognitive test system) in adults aged over 50 with PASC?

2.2 Secondary Research Questions

1. What is the impact of the ReaCT programme on cognition as measured using the FLAME cognitive test system in adults over 50, and over 18, with PASC?
2. What is the impact of the ReaCT programme on self-reported cognition, activities of daily living, mood, sleep, fatigue, and quality of life in adults over 50, and over 18, with PASC?
3. What is the impact of the ReaCT programme on healthcare and personal social care service utilisation and employment activity in adults over 50, and over 18, with PASC?
4. What is the impact of genotype and / or polygenic risk on treatment response to the ReaCT programme in adults over 50, and over 18, with PASC?

2.3 Outcome measures/endpoints

All outcome measures will be collected at six weeks and six months from a baseline assessment.

2.4 Primary endpoint/outcome

The primary outcome will be executive function at six months, measured using the well-validated verbal reasoning task. This task has been used in previous trials of cognitive training interventions and has good generalisability to other areas of cognition and function[17].

2.5 Secondary endpoints/outcomes

Secondary outcomes will be:

a. Cognition assessed using the FLAME cognitive test battery, which utilises validated tests of individual cognitive domains to capture cognitive performance across working memory, episodic memory, reaction time, attention and executive function. Key tests are digit vigilance, verbal reasoning, picture recognition, self-ordered search and digit span. It has established sensitivity to predict cognitive status across the early cognitive decline criteria published by the FDA and enables detection of cognitive change over time.
b. Self-reported cognition measured by the IQCODE that is clinically validated for detection of cognitive status[18]
c. Subjective cognitive impairment measured by the 24-item Subjective Cognitive Decline Questionnaire[19]
d. Quality of life measured by the EQ5D measure with EQ-VAS[19], based on the PHOSP-COVID study design[19]
e. Instrumental Activities of Daily Living measured by a modified self reported six-item IADL, based on the previous ReaCT trial, the Post-COVID Functional Status (PCFS) scale[20] and the Washington Group Short Set on Functioning (WG-SS)[20] to align with the PHOSP-COVID design [19];
f. Symptoms of mood and depression, measured by the nine-item Patient Health Questionnaire (PHQ-9)[19].
g. Symptoms of anxiety, measured by the seven-item Generalised Anxiety Disorder (GAD-7) scale[19];
h. Experience of fatigue measured by the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT) scale[27]. An additional question will capture the approximate time of day participants experience fatigue.
i. Sleep quality measured by the short-form Cognitron Online Sleep Monitoring Scale (COSMOS)
j. Health care and personal social care service usage will be captured using a modified version of the Client Service Receipt Inventory (CSRI) [28] to enable health economics analysis.
k. Within the CSRI, participants will be asked to provide brief details about their employment activity to support the health economic analysis and to capture changes in their employment activity post-COVID infection.
l. DNA sampling achieved through self-administered saliva sample kits.

2.6 Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To compare the effect of the ReaCT programme on executive function	• Verbal Reasoning task	• Baseline • Six months
Secondary Objectives 1) To compare the effect of the ReaCT programme on cognition, function, mood, fatigue, sleep, and quality of life	• FLAME Cognitive Test System • IQCode • Subjective Cognitive Decline Questionnaire • EQ5D Quality of Life measure • Modified 6-item Instrumental Activities of Daily Living • Post-COVID-19 Functional Status scale • Washington Group Short Set on Functioning • Patient Health Questionnaire-9 • Generalised Anxiety Disorder Scale -7 • Functional Assessment of Chronic Illness Therapy – Fatigue – Scale • Sleep Quality	• Baseline • Six weeks • Six months
2) To establish the cost-effectiveness of the ReaCT programme	• Modified Client Service Receipt Inventory • Employment activity • Residential status	• Baseline • Six weeks • Six months
3) To determine the role of defined genetic factors on cognition and treatment	• DNA sample collected at baseline	• Baseline

response in people in adults over 40, and over 18, with PASC		
Tertiary Objectives 1) To monitor safety of the ReaCT programme and the trial smartphone app and website	• Adverse Event and Serious Adverse Event reporting in response to push notification (on app) or email prompts (on web) or proactively by participants through the website, telephone or email	Continuous
2) To monitor compliance of users with the ReaCT programme	• Digital usage data capture (app and web-based platform)	Six months
3) To collect information about the user experience and feedback on the trial and smartphone app and website	• End of study exit survey • Feedback form	Continuous

3. TRIAL DESIGN

A six-month two-arm placebo-controlled double-blind online randomised controlled trial in 1608 participants.

4. TRIAL SETTING

The trial will be delivered remotely, with participants accessing the trial process, intervention and assessments through an app or web-based platform

5. PARTICIPANT ELIGIBILITY CRITERIA

5.1 Inclusion criteria

- Age 18 and over (primary analysis population: aged 50 and over).
- Self-reported Covid-19 infection (based on previous positive PCT/LFT test, laboratory /hospital diagnosis or suspected infection).
- Subjective Cognitive Impairment (based on self-report, supported by capture of symptoms and impacts).
- Access to a smartphone, tablet, or computer with an internet connection.
- Good understanding of the English Language, sufficient to participate.

*This study will be open to all to ensure diversity.

5.2 Exclusion criteria

- Already taking part in another active interventional clinical trial.
- Having accessed the ReaCT programme online through participation in the PROTECT UK ageing cohort at any time during the last 12 months.
- Diagnosis of dementia.

6. TRIAL PROCEDURES

6.1 Recruitment

6.1.1 Participant identification

Recruitment of participants will be achieved through a range of sources as detailed below:

6.1.1.1 Primary Care

Participants will be identified through existing primary care Clinical Research Network, community care and other NHS organisations with appropriate referral pathways. Patients will be pre-screened for the age criteria for this study and contacted by email and SMS via the direct care team. Surgeries will also display on-screen information about the trial. All participants will be signposted to the BEACON app download and web-based platform for registration.

6.1.1.2 PROTECT Study Cohort

Participants will also be identified through the PROTECT study cohort using an established 'Cohort Access Request' process. The PROTECT study operates entirely online, with existing participants receiving email reminders to log in and complete outcome assessments or register for new trials. All participants have given consent for contact and have full datasets for pre-screening. The PROTECT study has existing ethical approval (Ref: 13/LO/1578) and has been running since April 2015. The ReaCT programme is available to all PROTECT participants as an engagement mechanism. The cohort will be pre-screened for usage of the ReaCT programme. Participants who have not accessed the programme within the last 12 months will be invited by email and signposted to the BEACON trial app download or web-based portal.

6.1.1.3 COVID Symptom Study (CSS) Biobank

Participants in the COVID Symptom Study Biobank will be invited to take part in the BEACON trial via Biobank communications and cohort access processes. Participants will be pre-screened for previous positive COVID-19 infection as per the Biobank protocols and identified in the BEACON app by their unique CSS Biobank identifier.

6.1.1.4 Publicity and social media

National and regional publicity will be sought to raise the profile of the trial, with all messaging signposting potential participants to the BEACON app download or web-based portal. Targeted social media will also be employed using the same signposting route, including Facebook advertising and Twitter. Community pharmacies, care homes, dental clinics, eye

clinics, health clubs and gyms that indicate interest in advertising the study will be able to do so using the approved study poster. The poster will contain messaging signposting interested persons to the BEACON app or web-based portal.

6.1.1.5 Additional Recruitment Sources

In the event that additional recruitment is required new participants will be approached through NHS Trust clinics, the Exeter 10,000 cohort of older adults (existing approval and consent for contact) and through partner platforms such as Join Dementia Research (an online self-registration service that enables volunteers with memory problems, carers of those with memory problems and healthy volunteers to register their interest in taking part in research).

6.1.2 Onboarding and Consent

Potential participants will be signposted to download the BEACON trial app to their smartphone or tablet from their app store for free. Participants without app-ready technology will have the option of registering the taking part from a website. The functions and user journeys will be identical between the two routes, although the app will enable more engagement and navigation options for users.

Consent will be given by participants following an established online, electronic process as follows:

1. The app or website will first display the Participant Information Sheet in digital format with a downloadable format option. Participants will be required to tick a box to confirm they have read and understood the document.
2. Participants will then be presented with each consent item in the approved Consent Form. They will have to tick each item individually before they can proceed.
3. Once complete, participants will then tick a further tick-box on the same consent page to confirm they consent to take part in the study.
4. Finally, a separate confirmation step page will appear for participants to confirm that they are consenting on purpose. This process ensures consent cannot be given in error. All pages provide a function to cancel the registration and delete the information provided up to that step.
5. Consents will be time- and date-stamped electronically and stored on the study database, linked to study ID and pseudo-anonymised to allow for linkage to personal details in the event this information is required for future contact.

Participants will give consent for the BEACON trial team to request data from their recruitment source if relevant. This will enable exploratory analyses to be conducted within subgroups of the trial cohort to explore specific research questions within the data.

These will include:

1. PROTECT-UK study: Participants will provide their PROTECT-UK participant Registration ID and give consent for data sharing between BEACON and PROTECT. This data will provide longitudinal cognitive, health and genetic data from existing PROTECT participants and will also enable cross-validation of participant exposure to the ReaCT programme in PROTECT.

2. Covid Symptom Study Biobank data: Participants will provide their unique Biobank study identifier. This data will provide rich longitudinal Covid-related data from the period of the pandemic.
3. Primary care, community care and NHS organisations: All participants will provide their GP surgery details and NHS number and will be asked to consent to contacting their GP in relation to their participation in this study.

6.1.3 Screening

Participants will complete a screening questionnaire to confirm their eligibility to take part. This will consist of the following:

1. Confirmation of Covid status including date and confirmation method of Covid test, in addition to questions about their number of Covid infections, ongoing symptoms and vaccination status, using a dedicated questionnaire currently in use in the PROTECT study.
2. Assessment of their subjective cognitive impairment using the Subjective Cognitive Decline Questionnaire[19]
3. Record of their current usage of brain training programmes.

Participants will be asked to confirm whether they are current participants in the PROTECT study. If so, they will be asked to provide their Registration ID to identify if they have used the ReaCT programme in the previous 12 months. This will also enable removal of their access to the ReaCT programme in their PROTECT study account for the duration of their participation in the BEACON trial.

6.2 The randomisation scheme

Randomisation of participants will be achieved through a purpose-built algorithm embedded in the trial app. This functionality exists within the broader PROMOTE digital infrastructure hosted by the University of Exeter and will be tailored to account for the specific randomisation and stratification requirements of the BEACON study. This will occur after a participant has consented to take part in the trial. The randomisation algorithm will allocate participants randomly, but will stratify them by:

- Age (age brackets of five years)
- Gender
- Usage of brain training games (Yes / No)
- COVID severity (No hospitalisation / hospitalised / Intensive care admission)

6.3 Blinding

Treatment allocation of participants will be recorded electronically in the cloud-based database which is hosted by the University of Exeter. This will ensure that both participants and research team will be blind to allocation, thus removing any bias. Administrative staff on the trial helpdesk that have direct participant contact will not be involved in any data analysis to avoid any unconscious bias as a result of their contact. Similarly, the app and web developers involved in maintenance of the trial infrastructure will not be involved in any data analysis or interpretation.

6.4 Emergency unblinding

Emergency unblinding will be overseen by the authority of the TSC/DMEC. If emergency unblinding is required, the linked dataset will be accessed by an independent administrator from the PROMOTE digital team (outside of the direct BEACON team) using the participant identifier via the administration portal for the trial to reveal treatment allocation of the individual participant. Access permissions for the administration portal will be restricted to the BEACON Trial Manager, Coordinator and Administrator and a supporting administrator in the PROMOTE team (who will act as the independent administrator in the event of unblinding). Access to the administration portal does not automatically provide access to treatment allocation details, as this is password-protected information. Passwords for accessing this information will only be held by the Trial Manager, under the supervision of the Chief Investigator, and will only be approved for use where required for safety and unblinding procedures.

6.5 Baseline data

All data will be collected through the app- and web-based study platform. Assessments at baseline will be:

- Demographic data: Demographic characteristics: Age, sex at birth, gender (expanded question for inclusivity), ethnicity, marital status, education level, employment and NHS number.
- Screening assessments: As described in section 6.1.3
- All trial assessments: As described in section 6.6

6.6 Trial assessments

Assessments will be conducted at baseline, six weeks and six months. Participants will receive weekly automated emails notifying them that assessments are available to complete until they are completed or no longer available. The assessments will become available for completion one week before the assessment point and remain open for completion during the week of the assessment, making them available for two weeks in total. Missing data or late data will be accounted for within the analysis plan.

Table 6.1. Trial Assessment Outcomes: scoring basis, range, and interpretation

Outcome Measures	Basis of scoring	Outcome range	Interpretation
Primary Outcome			
Verbal Reasoning[21]	Verbal reasoning task where 24 statement image combinations – the true or false answer to these is recorded numerical as correct or incorrect producing four variables	**-90 to 90* for summary score (VERBTOT)** -90 to 90 for the total errors made (VERBERR) Total time taken (VERBTT) 0 to 100 percentage correct identification (VERBACC)	Higher score indicates better performance
Secondary Outcome			
Self-Ordered Search	Spatial working memory task where symbols are hidden in a grid and the user searches systematically for them. Level reached, time and errors made produce three variables	**0 to 40 for summary score (SEARCHTOT)** Total time taken (SEARCHTT) 0 to 40 for total errors made (SEARCHERR)	Higher score indicates better performance
Digit Span	Numerical working memory task where the user must immediately recall increasing lengths of digits. The test outputs three variables	**0 to 20 for summary score (SPANTOT)** Total time taken (SPANTT) 0 to 20 for total errors made (SPANERR)	Higher score indicates better performance
Delayed Picture Recognition	Episodic memory task where the user is shown a series of pictures of everyday items to remember. They are asked to recall the images and distinguish them from similar images they were not previously shown. The test outputs accuracy and reaction time variables for new, original and combined stimuli.	**0 to 100 for accuracy score (DPICACC)** **0 to 100 for accuracy score for original stimuli (DPICOACC)** 0 to 100 for accuracy score for new stimuli (DPICNACC) **250 to 30000 for reaction time score (DPICRT)** 250 to 30000 for reaction time score for new stimuli (DPICNRT)	Higher score on accuracy indicates better performance. Lower score on reaction time indicates better performance

		250 to 30000 for reaction time score for original stimuli (DPICORT) 250 to 30000 for reaction time score median for new stimuli (DPICNRTM) 250 to 30000 for reaction time score median for original stimuli (DPICORTM) 0 to 30000 for standard deviation of reaction time responses to all stimuli (DPICSD)	
Digit Vigilance	Attentional task that requires a user to correctly respond when a numerical stimulus appears on the screen in a rolling series of digits. The test outputs accuracy and reaction time variables, with standard deviation of reaction time showing most accurate assessment when used across different devices.	**0 to 100 for accuracy score (VIGACC)** **0 to 1500 for standard deviation of reaction time responses for all targets (VIGSD)** 0 to 999 for false alarms (responses falling outside of specified time window) (VIGFA)	Higher score on accuracy indicates better performance. Lower score on reaction time indicates better performance
IQCODE[18]	Designed to quantify improvement/worsening of memory of tasks 10 years ago versus current time. Scored 1 to 5	1 to 5 1 – Much improved 2 – A bit improved 3 – Not much change 4 – A bit worse 5 – Much worse	Lower score indicates better performance
Subjective Cognitive Decline Questionnaire[19]	26 items designed to quantify opinions of changes in brain function. Scored 0 to 1, 0 to 2 or 1 to 2	0 to 1 0 – No 1 – Yes And 0 to 2 0 – Never	Higher score indicates higher prevalence of subjective cognitive issues

		1 – Sometimes 2 – Always And 1 to 2 1 – Good 2 - Poor	
EQ-5D Scale[22]	EQ-5D is scored as total index score from 5 items and a separate VAS (thermometer) scale. The index score is obtained based on UK population values.	Index outcome range: -0.224 to 1.000 Thermometer (VAS): 0 to 100	Higher score indicates better health with index scores of zero: death; 1.00: perfect health; negative scores: health states worse than death
Instrumental Activities of Daily Living Scale	Activities with a difficulty rating and help needed rating. 23 items scored 0 to 2 as a difficult rating and 0 to 3 for how much help the person needed	Difficulty Rating: 0 – No difficulty 1 – Some difficulty 2 – Great difficulty Help needed rating: 0 – On my own 1 – With some help 2 – With full help 3 – Done by others 94 – Activity did not occur	Higher score indicates poorer function
Post-COVID-19 Functional Status Scale[20]	Comprised of 13 items designed to quantify covid severity and symptoms experienced. Scored 0 to 4	0 to 4 0 – No 1 – Hardly at all 2 – A little 3 – Quite a lot	Higher score indicates higher covid severity and symptoms

		4 – Yes, all the time	
Washington Group Short Set on Functioning[23]	5 items designed to quantify difficulty doing certain activities. Scored 0 to 3	0 to 3 0 – No, no difficulty 1 – Yes, some difficulty 2 – Yes, a lot of difficulty 3 – Cannot do it at all	Lower score indicates better health
PHQ-9[24]	9 items designed to quantify severity of low mood and 1 item designed to capture difficulty to carry out certain tasks if low mood reported. Scored 1 to 3 or 0 to 3	0 to 3 Each question possible answer: 0 – Not at all 1 – Several days 2 – More than half the days 3 – Nearly everyday 0 – Not difficult at all 1 – Somewhat difficult 2 – Very difficult 3 – Extremely difficult	Overall score for low mood. Higher scores indicate presence of low mood.
GAD-7[25]	7 items designed to quantify severity of anxiety and 1 item designed to capture difficulty carrying out certain tasks if anxiety reported. Scored 0 to 3	0 to 3 Each possible answer: 0 – Not at all 1 – Several days 2 – More than half the days 3 – Nearly every day 0 – Not difficult at all	Overall score for anxiety levels. Higher scores indicate higher severity of anxiety.

		1 – Somewhat difficult 2 – Very difficult 3 – Extremely difficult	
Functional Assessment of Chronic Illness Therapy-Fatigue-Scale[26]	14 items designed to quantify feelings about illness. Scored 0 to 4 or 1 to 5	0 to 4, 1 to 5 Each possible answer: 0 – Not at all 1 – A little bit 2 – Somewhat 3 – Quite a bit 4 – Very much 1 - Early morning (7-9.30am) 2 - Late morning (9.30-12pm) 3 - Early afternoon (12-2.30pm) 4 - Late afternoon (2.30-5.00pm) 5 - Early evening (5-7.30pm)	
Sleep Quality	Designed to quantify sleep quality and habits. Scored- 0 to 5 or 1 to 5	0 to 5 0 – Never 1 – Almost never 2 – Once or twice a week 3 – Several times a week 4 – Nearly every day 5 – Every day 1 to 5 1 – Very poor	Higher score indicates better sleep

		2 – Poor 3 – Average 4 – Good 5 – Very Good	
CSRI[27]	Designed to quantify services and resources used for health and wellbeing. Scored 0 to 1 or 1 to 6	0 to 1 0 – No 1 – Yes 1 to 6, 98 1 – NHS 2 – Social services (+Adult Social Care) or local council 3 – Voluntary organisation/charity 4 – Self-funded through own money 5 – Through a Direct Payment 6 – Other 98 – Don't know	Higher score indicates more services and resources used for health and/or wellbeing

6.6.1 Primary Outcome Assessment (Executive Function)

The primary outcome will be the Verbal Reasoning task assessing verbal reasoning. The Baddeley Grammatical Reasoning test correlates with measures of general intelligence and involves determining the accuracy of a series of grammatical statements about a picture. The outcome measure is the total number of trials answered correctly in 90 seconds, minus the number answered incorrectly.

At baseline participants will complete the test in duplicate within one week (at least 12 hours apart) to improve data quality. At six months participants will complete the test once only.

6.6.2 Secondary Outcome measures

All secondary outcome measures will be collected at baseline, six weeks and six months. The measures will be completed in the app or web-based portal.

Cognitive Measures (FLAME Test System)

Secondary cognitive measures will be assessed using the FLAME Cognitive Test System to measure cognition at all timepoints. At baseline participants will complete the battery in duplicate within one week (at least 12 hours apart) to improve data quality. At six weeks and six months participants will complete the battery once only. The test battery takes up to 45 minutes to complete (including the Verbal Reasoning task that is the primary outcome measure, described above). They can be completed on either a computer with a keyboard and mouse or a touchscreen device. Participants will be encouraged to complete the tests at the same time of day on each test occasion. A video explaining the tests will be shown prior to completion of the tests.

The tests are:

1. Picture Recognition Stage One: A series of 20 pictures of everyday scenes and objects is presented on the screen, at the rate of one picture every three seconds, for the participant to remember. The participant is instructed that the pictures will all be reshown later mixed with very similar ones.
2. Self-Ordered Search task assessing spatial working memory: Spatial Working Memory is measured through this widely used test. Participants search a series of on-screen boxes to find a hidden symbol. Once found, participants search for the symbol again, remembering that the symbol will never be hidden in the same box twice. The symbol is hidden in every box once per level. After successfully completing a level, a new level opens with more boxes to search than the previous level. The outcome measure is the average number of boxes in the successfully completed trials. Participants are allowed three errors before the test terminates.
3. Digit Span task assessing working memory: Digit Vigilance (DV) is measured through a version of the “digit span” task, which has been widely cited in the neuropsychological literature and used in many commercially available brain-training devices. A series of numbers is shown to the participant who then enters the numbers in the same sequence as they appeared using a number keypad. The test uses a ratchet-style approach in which each successful trial is followed by a new sequence that is one digit longer than the last and each unsuccessful trial is followed by a new sequence that is one digit shorter than the last. This allows an accurate estimate of digit span to be made quickly. The outcome measure is the average number of

digits in all successfully completed trials. Participants are allowed three errors before the test terminates.

4. Digit Vigilance: A target digit from 0 to 9 is randomly selected and constantly on the screen. Digits 0 to 9 are then presented one at a time at the rate of 150 per minute. The participant is required to respond using the right arrow key (keyboard) or touchscreen as quickly as possible every time a digit matches the target digit. The number of correct detections and the speed of the correct detections are recorded. The standard deviation of reaction time has been shown to be the most accurate measure of reaction time when this test is used across different devices. The outcome measure is speed and accuracy of response as a measure of attention and processing speed. The test terminates after a total of 450 digits is presented, with 15 target digits in each block of 150 digits.
5. Picture Recognition Stage Two: The original pictures plus 20 very similar distractor pictures are presented one at a time in a counterbalanced order. Half of the original pictures are presented prior to the very similar distractor versions, and half afterwards. For each picture the participant indicates whether it is the precise picture shown in Picture Recognition Stage One, by clicking or pressing the keyboard or screen respectively using their right finger if it was shown, and their left finger if it was not shown, as quickly and accurately as possible. Each picture remains on the screen until a response is made. The accuracy and speed of each response are recorded as a measure is attention and processing speed. The test terminates after the participant gives a response for all 40 pictures.
6. Grammatical Reasoning task assessing verbal reasoning: The Baddeley Grammatical Reasoning test correlates with measures of general intelligence and involves determining the accuracy of grammatical statements about a series of pictures. The outcome measure is the total number of trials answered correctly, minus the number answered incorrectly, as a measure of executive function. The test terminates after 90 seconds.

Non-Cognitive Measures

The following non-cognitive measures will be used at baseline, six weeks and six months:

1. Self-reported cognition measured by the IQCODE that is clinically validated for detection of cognitive status[18]
2. Subjective cognitive impairment measured by the 24-item Subjective Cognitive Decline Questionnaire[19]
3. Quality of life measured by the EQ5D measure with EQ-VAS[19], based on the PHOSP-COVID study design[19]
4. Instrumental Activities of Daily Living measured by a modified self reported six-item IADL, based on the previous ReaCT trial, the Post-COVID Functional Status (PCFS) scale[20] and the Washington Group Short Set on Functioning (WG-SS)[20] to align with the PHOSP-COVID design [19];
5. Symptoms of mood and depression, measured by the nine-item Patient Health Questionnaire (PHQ-9)[19].
6. Symptoms of anxiety, measured by the seven-item Generalised Anxiety Disorder (GAD-7) scale[19];
7. Experience of fatigue measured by the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT) scale[27]. An additional question will capture the approximate time of day participants experience fatigue.

8. Sleep quality measured by the short-form Cognitron Online Sleep Monitoring Scale (COSMOS)
9. Health care and personal social care service usage will be captured using a modified version of the Client Service Receipt Inventory (CSRI) [28] to enable health economics analysis.
10. Within the CSRI, participants will be asked to provide brief details about their employment activity to support the health economic analysis and to capture changes in their employment activity post-COVID infection.

6.7 DNA Sample Handling

Participants will provide a DNA sample through a self-administered saliva collection process. One saliva sample kit will be posted to each participant to self-administer at home. This is a very swift, simple and painless procedure. In the unusual circumstance where someone is unable to give a saliva sample participants will be offered a cheek swab or blood sample as an alternative option.

All participants will provide DNA samples through the Exeter Clinical Research Facility, in partnership with the international life sciences company, deCODE. Saliva kits will be posted to participants from the Exeter site and returned to the Clinical Research Facility. These will be sent in batches to deCODE under a dedicated agreement for DNA extraction and genotyping. If participants have already provided a DNA sample as part of their involvement in a linked cohort (for example, PROTECT-UK) they will not be required to provide a second sample. Anonymised genetic data will be shared through a data sharing agreement at the University of Exeter, utilising unlinked participant IDs to ensure data protection.

6.8 Withdrawal criteria

6.8.1 Withdrawal by participant

Participants are free to withdraw from the trial at any point without giving a reason. This can be achieved by selecting the withdrawal option on the app / study website or by contacting the study team by email or telephone. Participant withdrawal will lead to automatic withdrawal of the role of their study partner.

6.8.2 Withdrawal procedure

At the point of withdrawal participants will receive notification in the app and by email that they have been withdrawn. Participants will have the option to retain or destroy any identifying data stored within the study (i.e. email address, telephone number). This option will be given at the point of withdrawal. Minimal identifiable information will be retained to ensure a record of consent is kept. All anonymized data will also be retained. This will include all anonymized assessment data, genetic data and the anonymised extracted DNA sample.

6.9 End of trial participation

End of trial is defined as the last assessment point completed by the last participant to enrol in the study or two weeks after the last participant's last time point if the last assessments are not completed.

7. TRIAL TREATMENTS

7.1 Name and description of investigational product(s)

Reasoning Cognitive Training (ReaCT) programme. This is an online cognitive training programme designed to target reasoning and problem solving. It comprises six games that follow a published paradigm for cognitive training, and which have been shown to benefit cognitive maintenance in older adults.

Control programme: These will be the same series of six games built without the rachet learning programming in the ReaCT version.

7.2 Dosage schedules

Participants will be encouraged to access and play their allocated programme for at least three times a week, for at least ten minutes each time. This will not be a prescriptive instruction and participants will have unlimited access to the programme

7.3 Assessment of compliance with treatment

Monitoring of participant use of the ReaCT programme (and control programme) will be achieved through digital usage data capture. The app and web-based platform will record each login event, games played, play duration and score achievement. Activity will be monitored automatically and reviewed by study coordinator to support participant communication.

8. SAFETY MONITORING & REPORTING

8.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an intervention which is related to any dose administered to that participant. The phrase "response to an intervention" means that a causal relationship between an intervention and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the intervention qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
	•

NB: To avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

8.2 Operational definitions for SAEs

** Due to the low risk nature of this study and to avoid collection of data that is not relevant to answering the research questions, we will not routinely capture AEs. This decision has been ratified by the TMG/DMEC for this study.*

Serious Adverse Event (SAE)
An SAE must fulfil the following criteria:

- Hospitalisation, excluding admission for scheduled and elective surgery.
- Death.
- Life-threatening condition, excluding conditions already in an unstable state at registration.
- Persistent or significant disability/incapacity.
- Congenital anomaly/birth defect.

8.3 Recording and reporting of SAEs

All SAEs occurring from the time of **start of trial treatment** until the end of the trial treatment will be reported by participants using an online form on the app or web-based platform. Participants will be prompted to enter any details of events at each login event and encouraged to report any event proactively using the online form or by contacting the study team by telephone or email. All SAEs will be logged in the trial database.

Receipt of an SAE on the system will prompt review by the study team. SAEs will be reviewed by the Chief Investigator and/or a study doctor within 24 hours. The participant, and their GP where appropriate, will be contacted for follow-up and recommended action. The Sponsor will also be informed.

SAE actions and monitoring will be recorded electronically, including the following information

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken including any treatment received
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered anticipated.

Any change of condition or other follow-up information will be reported to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

Absent participant follow-up
If a participant who has entered the intention-to-treat cohort fails to complete any online activity on two consecutive timepoints they will be contacted by telephone by a

study administrator. The purpose of the call will be to verify the health and wellbeing of the participant. If any suspected SAE is detected this will prompt a report.

8.4 Safety monitoring for cognitive and mental health

Cognitive status would usually be monitored by a medical practitioner at a clinical visit using a clinical assessment tool such as the Mini-Mental State Examination (MMSE) or similar. Since this study is conducted remotely, cognitive ability of participants will be monitored through an existing algorithm that automatically contacts the study team when a participant's results meet the criteria for possible cognitive decline, and which has been validated in the PROTECT cohort. The algorithm is based on completion of three of the cognitive tasks in the FLAME battery (Paired Associate Learning, Self-Ordered Search, and Digit Span, described in section 6.6.2) which are considerably more sensitive to change than the MMSE. The data of any participant who has performed more than one standard deviation below age-matched norms on two cognitive tests in two consecutive assessments at the six-month timepoint will be reviewed by one of two named study doctors (Dr Sue Dyson / Professor Clive Ballard).

Similarly, any participant reporting suicidality or a consistent score on the Patient Health Questionnaire indicating clinical depression (Score >8) will also be reviewed by one of the study doctors.

If concerns are considered to be valid, the participant and their GP will be contacted by the study doctor to recommend further assessment.

8.5 Responsibilities

<u>Chief Investigator (PI), Trial Manager and clinical delegate (TMG member):</u>
Initial review of any SAEs when reported by a participant

1. Using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated
2. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within two working days of initial reporting.
3. Ensuring that SAEs are recorded and reported to the sponsor in line with the requirements of the protocol.
4. Central data collection and verification of SAEs
5. Reporting safety information to the oversight committees identified for the trial (Trial Management Group) according to the Trial Monitoring Plan.
6. The unblinding of a participant for the purpose of expedited reporting

<u>Trial Management Group (TMG):</u>

In accordance with the Trial Terms of Reference for the TSG, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

9. STATISTICS AND DATA ANALYSIS

9.1 Sample size calculation

The sample size for this trial is based on a between-group effect size of 0.3 for the over 50 age group. This is consistent with the previous clinical trial of the ReaCT programme and other cognitive training programmes such as ACTIVE[11,17]. At 90% power, for a 5% level of significance, this will require 235 participants per group (470 across both groups). Based on previous trials of cognitive training we anticipate a 30% attrition. Therefore a total of 670 participants will be recruited for the primary analysis population.

The trial will also open to adults aged 18-49 with a recruitment target of an additional 1000 patients completing the six months assessments. The nature of this trial, including the app-based delivery of the brain training programme, raises the possibility of considerable over-recruitment of participants. Exceeding the target sample size will be acceptable due to the scalability of the intervention which has no impact on cost.

9.2 Planned recruitment rate

Based on recruitment to trials previously delivered through this digital infrastructure PROTECT we anticipate a recruitment rate of at least 300 participants per month. A three-month recruitment window has been defined but will be extended following recruitment review if required.

9.3 Statistical analysis plan

Data analyses will be conducted and reported in accord with CONSORT guidelines for non-drug trials. The primary analysis will take a modified intention-to-treat approach based on a between-group comparison of intervention and control participants aged 50 or above at six months wo have completed at least one training session, adjusting for baseline outcome score. A full Statistical Analysis Plan will be developed and published as an Appendix of the published protocol.

For the genetic data, imputed genotypes will be analysed for association with a range of phenotypes including cognitive trajectory and treatment response under an additive genetic model using regression. Factors such as age, gender, and ancestry-informed principal components will be controlled for. Analysis will be implemented in PLINK and R. A competitive GSA that tests whether genes in a given set are more strongly associated with the phenotype in question compared with others, will be conducted in the event of evidence of SNP effects; a deviation from normal on the Q-Q plot will indicate this. The GSA will be performed using the MAGMA software[29], which is widely used and known to perform well. Only high quality imputed SNPs will be used and ancestry principal components will be included as covariates. To start off, SNPs will be annotated to genes based on genomic location. Gene analysis will then be conducted, which computes p-values for association between each gene and the phenotype. As a final step, we will conduct a gene-level analysis which takes as input the gene analysis p-values from the prior step and a file containing the

gene sets to be tested. Genes are then assigned to gene sets (also known as pathways) which will be tested for association with the phenotype. Gene sets will be curated manually and from publicly available databases. They will be limited in size between 10 and 200 genes to remove bias related to gene size (i.e. the higher likelihood of significance as a function of gene size) and to ensure biologically specificity of pathways. A multiple testing correction will be applied in MAGMA using a command to implement a permutation procedure that yields a corrected p-value in the output file. Polygenic scores will also be used to evaluate the extent of shared genetic risk across phenotypes.

10. DATA MANAGEMENT

10.1 Data collection tools and source document identification

10.2 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent.

10.3 Data Recording and Record Keeping

All data collected on the BEACON trial database will be stored in Microsoft Azure UK region SQL databases. Personally identifiable data will be stored separately and securely from information obtained from the research. The only way to link the two data sets will be to use an Azure service called KeyVault. There will be no means of linking the two data sets via the databases. Backup instances of the data will be created daily.

Only approved database developers will have access to personally identifiable data through the electronic database. A dedicated study administration portal will provide approved administration team access to the information required to liaise with participants, extract randomisation information for unblinding (see section 6.4) and follow up any Serious Adverse Events. The administration portal requires username and password login.

Data may also be downloaded from the data portal and stored alongside other study documents in password-protected databases, which only the study team will have access to. Any paper records (copies and/or original documents) deriving from or belonging to the study will be kept in a locked filing cabinet, in a locked room, in a secure building the University of Exeter Medical School. Where applicable, these records will be pseudonymised by physically obscuring any PII and replacing it with the participant's Results ID.

The anonymised dataset will be retained for 10 years after the end of the trial. Data will be made available for reuse based on the University of Exeter's Open Research Exeter (ORE) policy for open access.

Access to saliva samples, extracted DNA and, where applicable, genotyped data will be coordinated through the Exeter Clinical Research Facility and DeCODE according to the approved regulations and security arrangements for each facility. The BEACON CI will have full access to all DNA analysis data relating to this study. The Exeter Clinical Research Facility will not have rights and access to the saliva samples but are providing a secure storage facility prior to transferring the saliva samples to DeCODE. DNA-related datasets transferred to the BEACON team will be stored in password-protected databases located on UoE secure IT infrastructure, including password-protected, external hard drives designed for the storage of large datasets.

11. ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the WMA Declaration of Helsinki – Ethical principles for medical research involving human subjects 2013.

11.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

11.3 Approvals

This trial is subject to full NHS REC and HRA review. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial. All documentation relating to ethics and approvals will be retained in the Trial Master File/Investigator Site File. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

It is the Chief Investigator's responsibility to produce the annual reports as required and to notify the REC and Sponsor of the end of the trial. If the trial is ended prematurely, the Chief Investigator will notify the REC and Sponsor, including the reasons for the premature termination. Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

11.4 Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required), host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

11.5 Participant Confidentiality

Data protection processes will be fully compliant with the UK General Data Protection Regulation and Data Protection Act 2018. All investigators and staff will comply with UK GDPR with regards to the collection, storage, processing, destruction and disclosure of any personally identifiable information (PII) and will uphold the regulation's core principles.

All PII will be stored as per in a separate and encrypted participants database, stored on a cloud-based server provided by Microsoft Azure and held within the UK region. Unique participant IDs will be created for each participant, using an unrelated sequence of characters, and this will not be linked to the pseudo-anonymised results data held in a separate database.

Only approved database developers will have access to personally identifiable data through the master electronic database. A management portal will give the Chief Investigator, Professor Anne Corbett, and the delegated administration team, access to personal information where required for the trial. Access to PII will be limited to the administrator responsible for supporting participants. PII may also be stored in password-protected databases located on University of Exeter Secure Data Research Hub which only the study team at the University will have access to.

Access to PII outside of the master electronic database and management portal (i.e. paper copies and participant email correspondence to the BEACON helpdesk) will be limited to the Chief Investigator and the delegated administration/ managerial team. BEACON study clinicians may gain access to PII for the purpose of reviewing cognitive performance and mental health data (please see section 10.2).

In the event of a subject access request (SAR), the individual will be provided with the UoE Data Subject Request Form including the contact details for the University of Exeter Data Protection Officer and will be advised to submit their request in writing.

No PII data will be transferred to any other third party without written participant consent, and PII will not be included in any analysis files or study disseminations. PII will be stored for three years after the study has ended. It will then be destroyed. Pseudonymised and anonymised information will be kept indefinitely and up until the study objectives have been achieved. If the participant continues to be involved in the overall PROTECT host cohort their PII will be retained in the core PROTECT study participants database as per study protocols.

The data custodian for this trial is the Chief Investigator, Professor Anne Corbett (*a.m.j.corbett@exeter.ac.uk*).

11.6 Public and Patient Involvement

This study has benefitted from a number of PPI activities including consultation with a dedicated Lay Advisory Group. PPI will be delivered for this study through this group, which is a group of adults, most of whom have direct experience of cognitive impairment following COVID-19 infection. The group will meet every quarter and/or at key points throughout the study. The group will be consulted on major issues such as app design and delivery, recruitment and retention strategies. Members of the PPI group will be invited to raise any

discussion points with investigators. The group will be co-chaired by the Chief Investigator and Lay Investigator (Ms Frampton) to ensure full representation across the study. Where wider discussion with lay groups is deemed necessary the PPI group at the PenCLAHRC group, hosted at the University of Exeter, will be consulted and online channels available through the PROTECT study will be utilised.

11.7 Protocol compliance

Protocol compliance will be monitored by the Trial Manager and reviewed by the TMG. Deviations will be documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

11.8 Financial and other competing interests for the Chief Investigator, PIs at each site and committee members for the overall trial management

None

11.9 Indemnity

Indemnity will be covered by the standard insurance cover produced by the University of Exeter as Sponsor and as detailed in separate documentation.

11.10 Amendments

Substantial amendments will be approved by the TMG prior to request for Sponsor sign off and subsequent submission to the REC and notification to the HRA Amendments Team. Non-substantial amendments will be signed off by the Sponsor prior to submission to the HRA Amendments Team. No amendment will be actioned until full approval has been confirmed from local sites supporting the trial. Amendments will be recorded in Appendix A.

11.11 Access to the final trial dataset

Access to the trial dataset will be restricted to the TMG members. Applications for access to the dataset will be considered on a case-by-case basis by the TMG. There are no specific terms set by the funder for data access.

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APPENDIX

Online brain training for people with cognitive impairment following SARS-CoV-2 infection: A randomised controlled clinical trial (BEACON)

STATISTICAL ANALYSIS PLAN (SAP)

Trial Information

Trial full title	Online brain training for people with cognitive impairment following SARS-COV-2 infection: A randomised controlled clinical trial
Trial registration number	39864861
Trial Chief Investigator	Prof Anne Corbett
Trial Statistician	Dr Gareth Williams
Research Group	PROTECT Research Group

Document History

Version	**Date**	**Author**	**Comments/Change Details**
Draft v0.1	29th May 2025	Prof Anne Corbett / Shanice Tulloch	Initial draft
V1.0	1st September 2025	Prof Anne Corbett / Prof Clive Ballard	Full version

PREPATION OF THE STATISTICAL ANALYSIS PLAN

The statistical analysis plan SAP has been prepared in accordance with ICH-9 statistical guidelines for clinical trials[1] and JAMA Guidelines for the Content of Statistical Analysis Plans in Clinical Trials[2]. Results are to be reported in accordance with the CONSORT checklist for trials[3].

This SAP document is based on the trial protocol version 4.0.

This SAP covers the analysis plan for the clinical trial data. It does not cover the genetic analysis component of the trial which will be undertaken separately.

TRIAL INFORMATION

Aim: The aim of this study is to conduct a two-arm double-blind randomised controlled trial of the ReaCT cognitive training programme in adults with subjective or established cognitive impairment following infection with SARS-CoV-2 with a view to a future roll-out of the programme on a population-wide basis.

Design & randomisation: Two-arm placebo-controlled double-blinded randomised controlled trial in 670 participants completing a two-arm, six-month parallel group RCT. Participants will be randomised to intervention (REACT brain training games) or controlled (brain training games without the REACT component). Randomisation is stratified on participant age, frequency of existing brain training activity, COVID severity.

Primary Analysis Population: The primary analysis population will be participants completing at least one session of ReACT or control training sessions in a Modified Intention to treat Analysis (M-ITT).

Primary Research Question: What is the impact of the ReaCT programme on executive function as measured using the verbal reasoning task (part of the FLAME cognitive test system) in adults aged over 50 with PASC?

Secondary Research Questions: (1) What is the impact of the ReaCT programme on other aspects of cognition as measured using the FLAME cognitive test system in adults over 50 with PASC, and over 18, with PASC? (2) What is the impact of the ReaCT programme on self-reported cognition, activities of daily living, mood, sleep, fatigue, and quality of life in adults over 50, and over 18, with PASC? (3) What is the impact of the ReaCT programme on healthcare and personal social care service utilisation and employment activity in adults over 50, and over 18, with PASC? (4) What is the impact of genotype and / or polygenic risk on treatment response to the ReaCT programme in adults over 50, and over 18, with PASC?

Sensitivity Analyses

The same comparisons will be undertaken in the full intention to treat population and in the per protocol population.

Exploratory analysis

Further exploratory analysis will examine treatment response by the severity of PASC, will explore the treatment response according to the number of ReACT training sessions and will examine other potential predictors of treatment response.

Sample size: The sample size for this trial is based on a between-group effect size of 0.3 for the over 50 age group. This is consistent with the previous clinical trial of the ReaCT programme and other cognitive training programmes such as ACTIVE[4,5]. At 90% power, for a 5% level of significance, this will require 235 participants per group (470 across both groups). Based on previous trials of cognitive training we anticipate a 30% attrition. Therefore, a total of 670 participants will be recruited for the primary analysis population.

Outcome measures/endpoints

All outcome measures will be collected at baseline (pre-randomisation), 6 weeks and 6-months (post-randomisation). The outcomes collected, scoring and interpretation are summarised in Table 1.

STATISTICAL ANALYSIS

Timing & Conduct of Analysis

All analyses will be undertaken by a statistician blinded to group allocation.

Baseline Balance & Study Flow

To check baseline balance, summary statistics for baseline characteristics by groups will be reported and groups compared descriptively (Table 2). The flow of participants through the trial will be summarised in a CONSORT flow diagram. Demographic characteristics of participants who do not provide data for the primary outcome measure of their trial at follow-up will be set out (including participants who have formally withdrawn (but allowed their previously collected data to be used), and participants not formally withdrawn but did not complete the outcome at follow-up).

Analysis Methods

Descriptive

All primary and secondary outcomes will be reported descriptively (continuous: mean/SD & median/quartiles; binary: frequency, percentage) at all follow-up timepoints (Table 2).

Inferential analysis

The analyses will compare primary and secondary (continuous) outcomes between intervention and control groups at 6-month follow-up in individuals aged 50 and above. Analysis will use an ANOVA general linear model with adjustment for baseline outcome scores, age, gender and educational attainment level. Primary analyses will be based on a Modified Intention To Treat (ITT) approach for patients completing at least one training session and will use observed data only (no imputation will be used). The same analysis approach will be used for secondary outcomes (Table 3).

Reporting of Results

The results of all descriptive and inferential analyses for the primary and secondary continuous outcomes are set out in dummy tables. All inferential results will be reported as between group mean differences (for continuous outcomes) or relative risks (for binary outcomes) with 95% confidence intervals. No formal adjustments of p-values for multiple testing will be performed; the results for the

primary outcome will be interpreted first and the results of the secondary outcomes will then be interpreted in the light of multiple testing.

Adverse Events

Data on adverse events will be set out descriptively by trial arm (Table 4). Each reported adverse event will be independently assessed by the TSC to adjudicate whether the adverse event was related to (i) trial processes; or (ii) the intervention if in the intervention arm.

Table 1. Outcomes: scoring basis, range, and interpretation

Outcome Measures	Basis of scoring	Outcome range	Interpretation
Primary Outcome			
Verbal Reasoning[6]	Verbal reasoning task where 24 statement image combinations – the true or false answer to these is recorded numerical as correct or incorrect producing four variables	**-90 to 90* for summary score (VERBTOT)** -90 to 90 for the total errors made (VERBERR) Total time taken (VERBTT) 0 to 100 percentage correct identification (VERBACC)	Higher score indicates better performance
Secondary Outcome			
Self-Ordered Search	Spatial working memory task where symbols are hidden in a grid and the user searches systematically for them. Level reached, time and errors made produce three variables	**0 to 40 for summary score (SEARCHTOT)** Total time taken (SEARCHTT) 0 to 40 for total errors made (SEARCHERR)	Higher score indicates better performance
Digit Span	Numerical working memory task where the user must immediately recall increasing lengths of digits. The test outputs three variables	**0 to 20 for summary score (SPANTOT)** Total time taken (SPANTT) 0 to 20 for total errors made (SPANERR)	Higher score indicates better performance

Delayed Picture Recognition	Episodic memory task where the user is shown a series of pictures of everyday items to remember. They are asked to recall the images and distinguish them from similar images they were not previously shown. The test outputs accuracy and reaction time variables for new, original and combined stimuli.	**0 to 100 for accuracy score (DPICACC)** **0 to 100 for accuracy score for original stimuli (DPICOACC)** 0 to 100 for accuracy score for new stimuli (DPICNACC) **250 to 30000 for reaction time score (DPICRT)** 250 to 30000 for reaction time score for new stimuli (DPICNRT) 250 to 30000 for reaction time score for original stimuli (DPICORT) 250 to 30000 for reaction time score median for new stimuli (DPICNRTM) 250 to 30000 for reaction time score median for original stimuli (DPICORTM) 0 to 30000 for standard deviation of reaction time responses to all stimuli (DPICSD)	Higher score on accuracy indicates better performance. Lower score on reaction time indicates better performance
Digit Vigilance	Attentional task that requires a user to correctly respond when a numerical stimulus appears on the screen in a	**0 to 100 for accuracy score (VIGACC)**	Higher score on accuracy indicates better performance.

	rolling series of digits. The test outputs accuracy and reaction time variables, with standard deviation of reaction time showing most accurate assessment when used across different devices.	**0 to 1500 for standard deviation of reaction time responses for all targets (VIGSD)** 0 to 999 for false alarms (responses falling outside of specified time window) (VIGFA)	Lower score on reaction time indicates better performance
IQCODE[7]	Designed to quantify improvement/worsening of memory of tasks 10 years ago versus current time. Scored 1 to 5	1 to 5 1 – Much improved 2 – A bit improved 3 – Not much change 4 – A bit worse 5 – Much worse	Lower score indicates better performance
Subjective Cognitive Decline Questionnaire[8]	26 items designed to quantify opinions of changes in brain function. Scored 0 to 1, 0 to 2 or 1 to 2	0 to 1 0 – No 1 – Yes And 0 to 2 0 – Never 1 – Sometimes 2 – Always And 1 to 2 1 – Good 2 - Poor	Higher score indicates higher prevalence of subjective cognitive issues

EQ-5D Scale[9]	EQ-5D is scored as total index score from 5 items and a separate VAS (thermometer) scale. The index score is obtained based on UK population values.	Index outcome range: -0.224 to 1.000 Thermometer (VAS): 0 to 100	Higher score indicates better health with index scores of zero: death; 1.00: perfect health; negative scores: health states worse than death
Instrumental Activities of Daily Living Scale	Activities with a difficulty rating and help needed rating. 23 items scored 0 to 2 as a difficult rating and 0 to 3 for how much help the person needed	Difficulty Rating: 0 – No difficulty 1 – Some difficulty 2 – Great difficulty Help needed rating: 0 – On my own 1 – With some help 2 – With full help 3 – Done by others 94 – Activity did not occur	Higher score indicates poorer function
Post-COVID-19 Functional Status Scale[10]	Comprised of 13 items designed to quantify covid severity and symptoms experienced. Scored 0 to 4	0 to 4 0 – No 1 – Hardly at all 2 – A little 3 – Quite a lot 4 – Yes, all the time	Higher score indicates higher covid severity and symptoms
Washington Group Short Set on Functioning[11]	5 items designed to quantify difficulty doing certain activities. Scored 0 to 3	0 to 3 0 – No, no difficulty 1 – Yes, some difficulty 2 – Yes, a lot of difficulty	Lower score indicates better health

		3 – Cannot do it at all	
PHQ-9[12]	9 items designed to quantify severity of low mood and 1 item designed to capture difficulty to carry out certain tasks if low mood reported. Scored 1 to 3 or 0 to 3	0 to 3 Each question possible answer: 0 – Not at all 1 – Several days 2 – More than half the days 3 – Nearly everyday 0 – Not difficult at all 1 – Somewhat difficult 2 – Very difficult 3 – Extremely difficult	Overall score for low mood. Higher scores indicate presence of low mood.
GAD-7[13]	7 items designed to quantify severity of anxiety and 1 item designed to capture difficulty carrying out certain tasks if anxiety reported. Scored 0 to 3	0 to 3 Each possible answer: 0 – Not at all 1 – Several days 2 – More than half the days 3 – Nearly every day 0 – Not difficult at all 1 – Somewhat difficult 2 – Very difficult 3 – Extremely difficult	Overall score for anxiety levels. Higher scores indicate higher severity of anxiety.
Functional Assessment of	14 items designed to quantify feelings about illness. Scored 0 to 4 or 1 to 5	0 to 4, 1 to 5 Each possible answer:	

Chronic Illness Therapy-Fatigue-Scale[14]		0 – Not at all 1 – A little bit 2 – Somewhat 3 – Quite a bit 4 – Very much 1 - Early morning (7-9.30am) 2 - Late morning (9.30-12pm) 3 - Early afternoon (12-2.30pm) 4 - Late afternoon (2.30-5.00pm) 5 - Early evening (5-7.30pm)	
Sleep Quality	Designed to quantify sleep quality and habits. Scored- 0 to 5 or 1 to 5	0 to 5 0 – Never 1 – Almost never 2 – Once or twice a week 3 – Several times a week 4 – Nearly every day 5 – Every day 1 to 5 1 – Very poor 2 – Poor 3 – Average 4 – Good 5 – Very Good	Higher score indicates better sleep

CSRI[15]	Designed to quantify services and resources used for health and wellbeing. Scored 0 to 1 or 1 to 6	0 to 1 0 – No 1 – Yes 1 to 6, 98 1 – NHS 2 – Social services (+Adult Social Care) or local council 3 – Voluntary organisation/charity 4 – Self-funded through own money 5 – Through a Direct Payment 6 – Other 98 – Don't know	Higher score indicates more services and resources used for health and/or wellbeing

Table 2 (dummy) Baseline Characteristics

Characteristics	**REACT Brain Training Games N=**	**Placebo Brain Training Games N=**
Age (18-50)		
Age (50+)		
Gender		
Education level		
Covid experience		

Table 3 – (dummy) Primary Analysis: comparison of groups at 6-month follow-up

	REACT Brain Training Group		Placebo group		Between group difference*	
	Baseline	6-months	Baseline	6-months		
	N mean SD	N mean SD	N mean SD	N mean SD	Mean (95% CI), P-value	
Primary Outcome						
Verbal Reasoning (VERBTOT)						
Secondary Outcome						
Self-Ordered Search (SEARCHTOT)						
Digit Span (SPANTOT)						
Delayed Picture Recognition (DPICACC)						
Delayed Picture Recognition (DPICOACC)						
Delayed Picture Recognition (DPICRT)						
Digit Vigilance (VIGACC)						
Digit Vigilance (VIGSD)						

IQCODE						
Subjective Cognitive Decline Questionnaire						
EQ-5D Scale						
Instrumental Activities of Daily Living Scale						
Post-COVID-19 Functional Status Scale						
Washington Group Short Set on Functioning						
PHQ-9						
GAD-7						
Functional Assessment of Chronic Illness Therapy-Fatigue-Scale						
Sleep Quality						
CSRI						

*adjusted for baseline score and stratification variables

Table 4 – (dummy) adverse events and serious adverse events at 6-months follow-up

Adverse Events	**REACT BT Games**	**Control BT Games**
xxx	n/N (%)	n/N (%)
xxx	n/N (%)	n/N (%)
etc		
Serious adverse events		
xxx	n/N (%)	n/N (%)
xxx	n/N (%)	n/N (%)

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