STUDY TITLE: Improving wellbeing Associated with Rare Familial dementias (IWARF)**.**

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Acronyms and abbreviations

AAO	Anticipated Age of Onset
ACT	Acceptance and Commitment Therapy
ADAPT	UCL Ageing, Dementia And Psychological Therapies (ADAPT) Lab
AE	Adverse event
ANCOVA	Analysis of covariance
BNF	British National Formulary
CACE	Complier average causal effect
CADR	Centre for Ageing and Dementia Research
CICI	Context and implementation of complex interventions
Co-I	Co-Investigator
CRF	Case report form
CTU	Clinical Trials Unit
DMEC	independent Data Monitoring and Ethics Committee
DRC	Dementia Research Centre
EBE	Experts by experience
EQ-5D-5L	European Quality of Life 5 Dimensions 5 level version
FAD	Familial Alzheimer's disease
FFTD	Familial frontotemporal dementia
FTD	frontotemporal dementia
GAD7	Generalized Anxiety Disorder scale (7 items)
GCP	Good Clinical Practice
GENFI	The Genetic Frontotemporal Initiative
GNMLD-TALK	Psychosocial support for people affected by Genetic and Non-Memory Led Dementias: developing digital provision and understanding the role of existing TALKing therapy services (GNMLD-TALK).
HCEC	Health and Care Economics Cymru
ICECAP-A	ICEpop CAPability measure for Adults
IQR	interquartile range
ISRCTN	International Standard Randomised Controlled Trial Number
IT	Information technology
ITT	Intention to treat
IWARF	Improving wellbeing Associated with Rare Familial dementias
MPFI	Multidimensional Psychological Flexibility Inventory
MRC	Medical Research Council
MS	Microsoft
NHS	National Health Service
NIHR	National Institute for Health Research
NPT	Normalisation process theory
NWORTH	North Wales Organisation for Randomised Trials in Health
ONS	Office of National Statistics
PAGIS	Psychological Adaptation to Genetic Information Scale
PaLS	Psychology and Language Sciences
PC	personal computer

PGD	Pre-implantation genetic diagnosis
PHQ9	Patient Health Questionnaire-9
PI	Primary Investigator
PIS	Participant Information Sheet
PPI	Patient and public involvement
PSSRU	Personal Social Services Research Unit
QA	Quality assurance
QALY	quality-adjusted life-year
QC	Quality control
RA	Research Assistant
RCT	Randomised controlled trial
RDS	Rare Dementia Support
REC	research ethics committee
SAE	Serious adverse event
SAP	statistical analysis plan
SCHE	Swansea Centre for Health Economics
SD	standard deviation
SOP	Standard operating procedure
SUS	System Usability Scale
T0 / T1 / T2	Baseline (Time 0) / post-intervention (Time 1) / follow up (Time 2)
TAU	treatment as usual
TMF	Trial master file
TMG	Trail management group
TSC	Trial steering committee
UCL	University College London
UCLA	University of California Los Angeles
UK	United Kingdom
WEMWBS	Warwick-Edinburgh Mental Wellbeing Scale
WP	work package
YOAD	Young onset Alzheimer's disease

Document History

This table below indicates a record of the changes, revisions, and updates made to the protocol over time, including and subsequent to the submitted protocol (Version 1.0).

Updated Version no.	Effective date	Authorship	Section changed	Summary of changes
1	30/08/2024	EB, EH, JS, AT	N/A	N/A
2	17/10/24	EB, EH, JS, AT	Added ISRCTN reg number	Added ISRCTN reg number

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1. BACKGROUND AND RATIONALE

1.1 Research context

This clinical trial is work package WP3c of the Rare Dementia (RD)-TALK study (full study title: Psychosocial support for people affected by Genetic and Non-Memory Led Dementias: developing digital provision and understanding the role of existing TALKing therapy services (GNMLD-TALK)). This study is a £1.9m research project carrying out a major investigation of the use of digital technology and support platforms (including their cost effectiveness) to facilitate tailored support to people with a lived experience of a rare dementia, giving flexibility around when and where support is accessed and overcoming geographical limitations. The GNMLD-TALK study is a five-year collaboration between University College London (UCL), Bangor University, Swansea University and King's College London, led by Prof. Joshua Stott from the Department of Psychology and Language Sciences, and director of the ADAPT Lab at UCL. The study aims to examine existing psychosocial provision and remotely-provided blended person-digital interventions. WP3c is a workstream within one of the 4 work packages, consisting of a randomised control trial to examine whether one program, developed and feasibility-tested under the UCL-led GENetic Frontotemporal Initiative (GENFI) study, improves psychological outcomes versus treatment as usual (TAU) in people living at-risk of inheriting either familial Alzheimer's Disease (FAD) or familial Frontotemporal Dementia (fFTD).

Note on the structure of this protocol

For the purposes of this Protocol, the randomised controlled trial will be outlined first, and the process evaluation second. The randomised controlled trial will henceforth be referred to as the "trial".

1.2 Brief review of published evidence

Individuals at-risk of familial frontotemporal dementia (fFTD) and familial Alzheimer's disease (FAD) have high psychological morbidity (Devenney et al., 2018). They report struggling with guilt and anxiety about risk to themselves and their children, decisions about whether to get tested, uncertainty about onset of symptoms, and see their risk as a barrier in life (Lewit-Mendes et al., 2018). Ongoing work led by our research group (papers in preparation) suggests that these psychological difficulties also affect their ability to participate and remain in clinical drug trials, compromising the development of new treatments.

Despite this high psychological morbidity, and the deleterious consequences of it (García-Toro et al., 2020), there are no tailored interventions available to support these at-risk groups, no systematic reviews/PubMed hits have examined blended person/digital interventions to support people with the psychological consequences of living at-risk of genetic dementias.

Supervising legacy-funded doctoral work, co-applicant Rohrer and PI Stott have co-developed (with EBE) a brief blended person/digital intervention informed by Acceptance and Commitment Therapy (Hayes et al., 2013) to support individuals at-risk of familial frontotemporal dementia. Development work was guided by MRC frameworks (Craig et al., 2008), already-conducted qualitative work (n=16 individuals at-risk), related literature from Huntington's disease, and expert psychologist/genetic counsellor input. The intervention, initially titled "Improving Wellbeing for people At-risk of Familial FTD" (IWARF) has undergone initial feasibility testing, outlined in Harding et al., (2024), to refine the intervention and identify the primary outcome(s). The current protocol describes the plan for a definitive full trial of the Better Living with Non-memory-led Dementia study, called "Improving wellbeing Associated with Rare Familial dementias (IWARF)".

2. TRIAL OBJECTIVES AND OUTLINE

2.1 Trial objectives and design

We will:

1. Test the effectiveness of the IWARF intervention in improving wellbeing and psychological outcomes [*WS1a*], including an internal randomised control pilot study recruiting people with fFTD only to the main trial in the first instance [*WS1b*]; and
2. Conduct a mixed methods process evaluation to elucidate mechanisms of change, barriers and facilitators to access and implementation as well as perceived benefits and costs [*WS2*].

The design is a pragmatic, two-arm randomised waiting list control trial with an 8-week intervention and 6-month follow-up comparing intervention to TAU with an internal 9-month pilot, and embedded process evaluation. The intervention comprises 8 learning modules (including module-end real-life tasks to put skills into practice) and up to three virtual check-in sessions with a facilitator. Intervention adaptation, adaptation to design and selection of primary outcome measures was based on feasibility work (Harding et al., 2024).

2.2 Trial expected duration

Recruitment will begin in October 2024, with data collection taking place until 31 March 2027. Analysis will take place over the subsequent 6 months (from April 2027 to September 2027). Please see the project Gantt chart here.

2.3 Trial flowchart

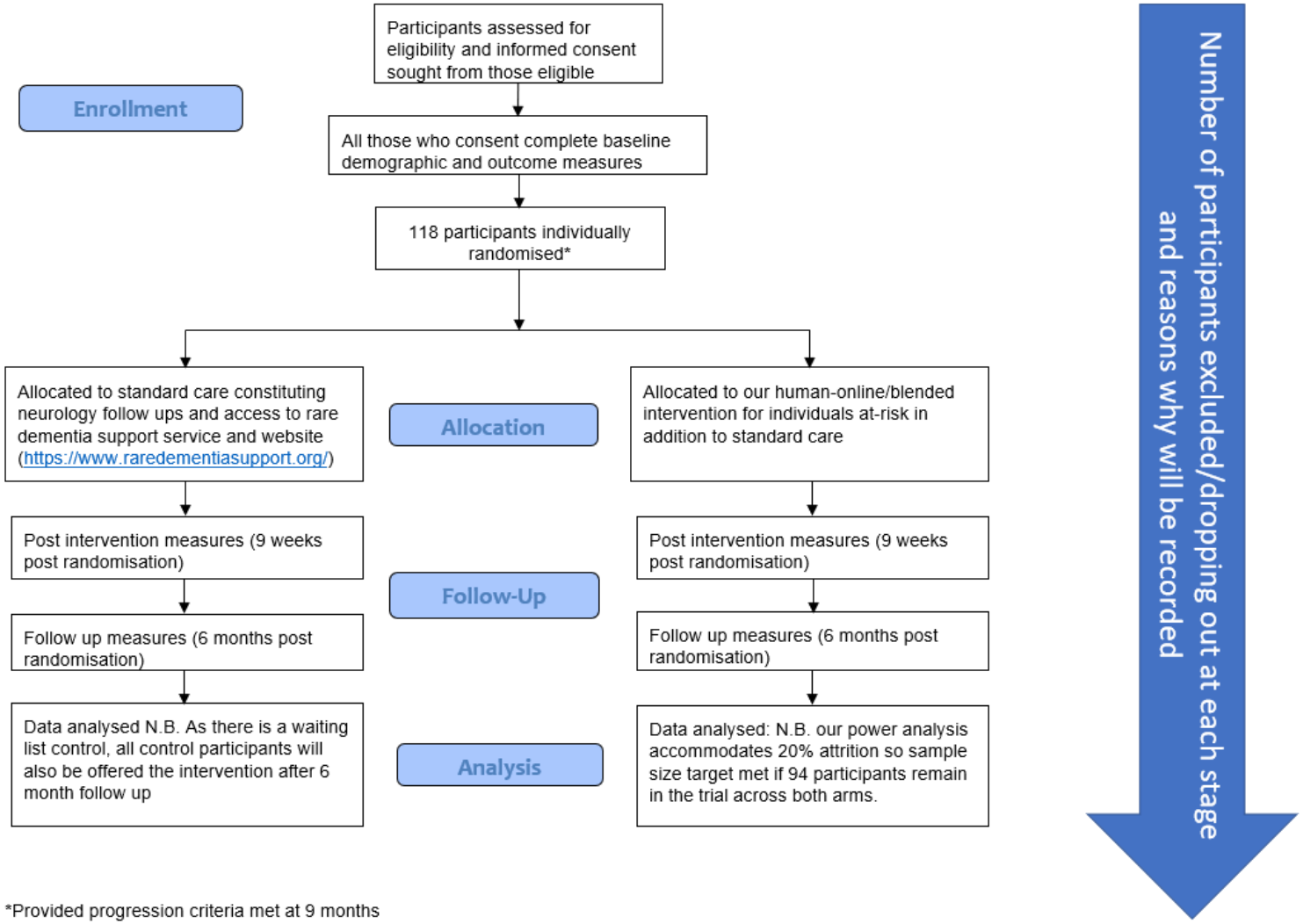


Figure 1. Adapted CONSORT Flow diagram showing flow through RCT in WP3c (intervention for individuals at-risk)

3. SELECTION AND WITHDRAWAL OF TRIAL PARTICIPANTS

3.1 Study population

Individuals eligible for this trial will be those who have a first degree relative who is symptomatic and/or are a known mutation carriers, who will be identified as such by virtue of one of the following:

1. At-risk of inheriting one of these conditions (e.g. they have not received genetic testing and so their genetic status for a familial dementia is unknown);

2. Tested positive for having the gene and will inherit FAD/fFTD (gene-positive);

3. Tested negative for having the gene and will not inherit FAD/fFTD (gene-negative).

3.1.1. Inclusion criteria:

- 18+ with a first degree relative who is symptomatic and/or are a known mutation carrier.
- Capacity to consent to research.
- Access to an internet enabled device.

3.1.2. Exclusion criteria:

- Individual is below the age of 18
- Individual does not have a first degree relative who is symptomatic and/or are a known mutation carrier.
- Individual reports to the trial team to be displaying symptoms of FAD/fFTD before enrollment
- Individual does not have capacity to consent to research
- Individual does not have access to an internet enabled device.

3.2 Recruitment sources and consent

The main study population comprises people with a family member living with an inheritable form of dementia (either familial Alzheimer's disease (FAD) or familial Frontotemporal Dementia (fFTD)). These individuals will be identified by virtue of being either:

- Research participants listed on research study registers within institutional databases (e.g. Dementia Research Centre, UCL). Individuals who have signed a Data Protection Act form and consented to be included on the Dementia Research Centre research register. These individuals have all opted to receive information about research opportunities.

OR

- Members of Rare Dementia Support who have opted into the RDS membership database. In opting to be listed on the RDS database, members understand that they may also be contacted about opportunities to participate in research we are

undertaking. These individuals will be contacted via email addresses already held by RDS and it will be made clear to them that they have a choice to participate or not and that not participating will not affect their membership of RDS in any way. Participation status for each RDS member will be documented alongside their internal-facing membership profile which is only accessible to RD talk study researchers and the RDS service team. RDS receives between 60 and 100 referrals per month, the limited sample of whom are likely to meet inclusion criteria based on knowledge at sign-up will be invited to participate in the clinical trial. As part of RDS external communications, we may be in touch with other institutions to promote the RDS service supporting families affected by fFTD/FAD, and encourage these institutions to signpost individuals to the RDS service. These individuals may be engaged in other support groups (e.g. national support network members known to Swansea/King's College London/Bangor co-investigators). As part of becoming a member of the RDS network, these individuals opt in to hear about opportunities to take part in research, which will include the IWARF study. We will also encourage participants to promote the study to their family members who may not yet be known to us, but who may wish to take part.

Where necessary to increase accessibility to the research project, study information and an opportunity for interested potential participants to contact the research team can be provided on relevant website pages (e.g. https://www.raredementiasupport.org/; www.adaptlab.net/rdtalk; www.ucl.ac.uk/drc/rd-talk) and affiliated online platforms (e.g. social media pages/collaborator websites).

3.2.1 Trial consent procedure

The baseline survey link will contain a link to the PIS in the homepage, an opt-in box to indicate consent to screening, and a full consent form to indicate consent to taking part in the full study (see 'Consent').

All participants will receive a link via email to a Qualtrics™ page comprising a short opt-in consent tickbox to agree to answer screening questions pertaining to the inclusion and exclusion criteria above. This will establish individuals' suitability for inclusion in this study. If an individual is screened as eligible, they will be directed to a full study online consent process to take part in the study which will subsequently take them to the baseline measures. If an individual is screened as ineligible, they will be directed to a page thanking them for their interest in the study and providing contact to the RDS service in case they wish to reach out for support.

3.2.2. Process evaluation consent process

Initially all participants will be invited to take part in the process evaluation interview when participants finish the completion of measures. Once a number (around 10-20) have agreed, a decision will be made (based on n needed) as to whether to continue whole population sampling or to conduct purposively sampling based on gene carrier status and disease type as well as relevant demographics (e.g., gender). Participants who agree to take part in this element of the study will be presented with a separate process evaluation participant information sheet (IWARF_Process_Eval_PIS_[V2 22/12/23]) and then a researcher will arrange one of the following consent processes (separate to the initial Trial consent process) in accordance with the participant's preference (see Figure 2):

1. Arrange a videoconference or telephone call whereby they will go through the consent form (IWARF_Process_Eval_CF_VX [V1 22/08/23]) which will be recorded as a record of consent. This has been previously approved (e.g. 8545/004: Rare Dementia Support Impact Study and 8545/007: Living Better with Rare Dementias: Testing blended person/digital intervention for carers of rare dementia to improve psychological outcomes);
2. Send the consent form via email to the participant which the participant will complete and return via email;
3. Send the consent form via post to the participant with a prepaid envelope which the participant will complete and return via post.

3.3 Randomisation procedure

118 participants will be randomly allocated with 1:1 allocation to the intervention or waiting list control group plus direction to TAU (for the context of this trial, the rare dementia support website).

Randomisation will be provided via secure online platform hosted by NWORTH CTU, Bangor University. Once consent and baseline measures have been completed the participant can be entered into the randomisation system. A dynamic adaptive randomisation algorithm (Russell et al., 2011) will be used to maintain the allocation ratio of 1:1 and balanced within stratification variables. Randomisation will be stratified by diagnosis (i.e., FAD, fFTD), and at-risk status (i.e. known mutation carrier, known non-carrier, unknown).Randomisation will be performed by a member of the Trial Management Committee after the participant completes the baseline assessment. The randomisation system will allow the user to check entry details (e.g., participant ID and stratification variable data) before randomisation is performed. A simple blinded confirmation email will be sent to the person who performed the randomisation and the chief investigator. Randomisation will be performed by a member of the Trial Management Committee after the participant completes the baseline assessment. The randomisation system will allow the user to check entry details (e.g., participant ID and stratification variable data) before randomisation is performed. A simple blinded

confirmation email will be sent to the person who performed the randomisation and the chief investigator.

The randomisation system will send a second unblinded email to the Trial Lead (EH) and Research Assistant(s) supporting them, informing them of all randomisations performed and the group allocations. They can then inform the participant of their allocation to either the intervention or comparison arm of the study. This will be done by emailing the details contained in the randomisation letter template (uploaded as part of research ethics submission).

Randomisation will be achieved by secure web access to the remote randomisation centre at NWORTH, Bangor University. The randomisation system will be set up, maintained, and

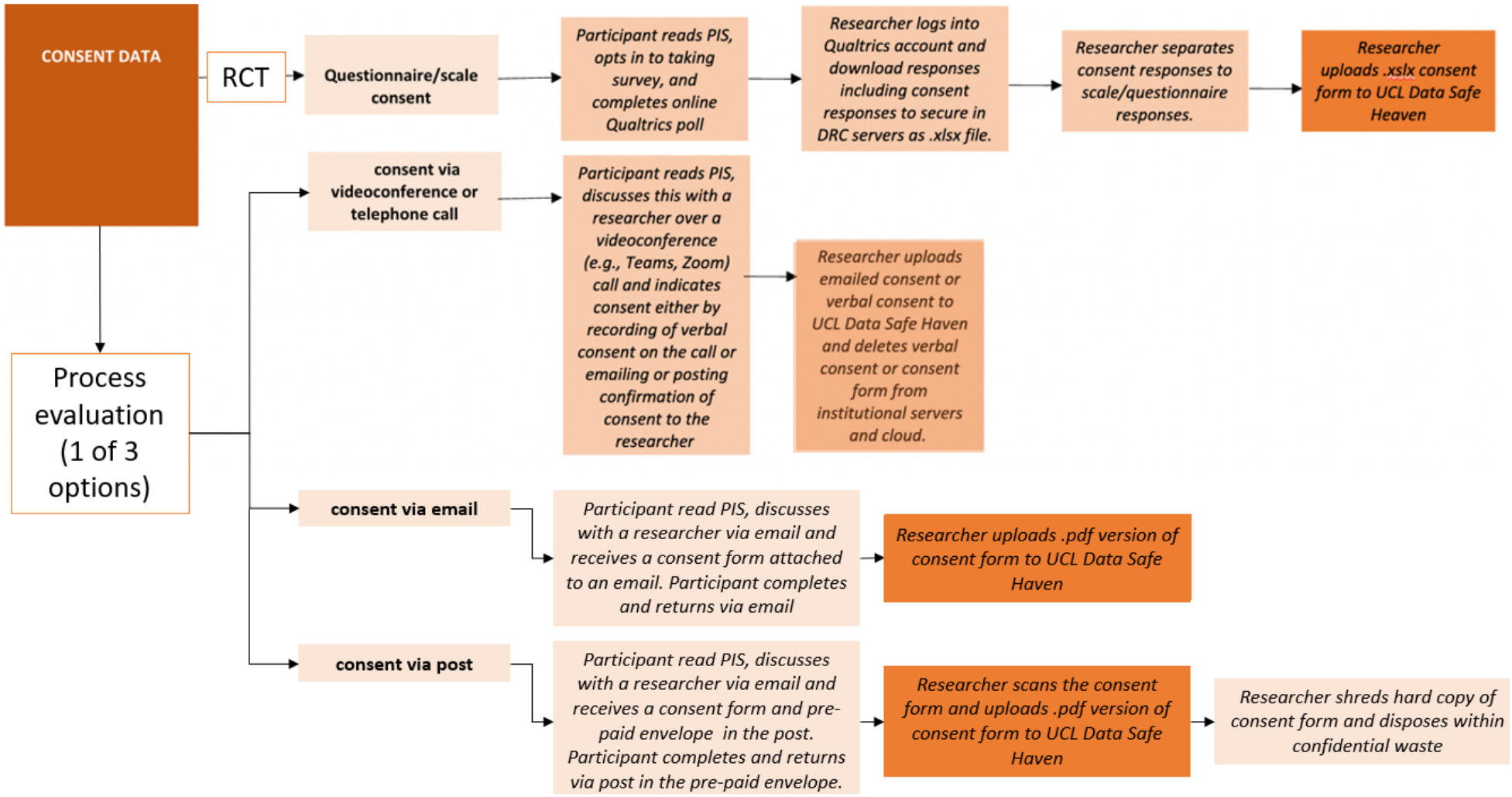


Figure 2. Information flow for consent process

monitored independently of the trial statistician or other trial staff. A detailed randomisation specification will be drawn up prior to set up of the system that will detail the technical system requirements, this will be guided by NWORTH's Standard Operating Procedures (SOPs) and approved by the Chief Investigator.

3.4 Unblinding procedure

It is not possible to blind the individual participants in this trial, but the Chief and Co-Investigators, health economists, programme manager and trial statistician will remain blind until the blinded analysis detailed in the Statistical Analysis Plan has been conducted and reported to the trial team. Unblinding will be performed following procedures outlined in NWORTH SOPs. The trial lead, IT specialist and Research Assistants will be unblinded.

3.5 Blinding Status of Study Roles within the Trial

Role in Study	**Blinded Stata**
Chief Investigator & Principal Investigators	Blinded
Trial Lead	Unblinded
Study's programme Manager	Unblinded
Trial Management Committee Member performing randomisation	Blinded
Trial Statistician	Blinded
IT Specialist	Unblinded
Research Assistants	Unblinded
Health economists	Blinded

3.6 Withdrawal of participants

Participants are free to withdraw at any time during the trial without any impact on their future health and care. Participant data collected to the point of withdrawal will be retained and may be used in the analysis set.

4. TRIAL PROCEDURES

4.1 Planned intervention

Following consent, baseline measures and randomisation, the intervention group will receive the Improving wellbeing Associated with Rare Familial dementias (IWARF) programme, an 8-week intervention comprising 8 online modules with additional psychoeducational videos. Modules cover issues identified as important in intervention development (e.g., rumination about risk or positive genetic status; uncertainty; making the most of life at-risk; isolation).

Issues known to be pertinent to at-risk individuals are addressed using a mixture of materials (e.g. videos and independent activities) most drawing on Acceptance and Commitment Therapy (e.g., using mindfulness-based acceptance techniques to manage rumination; see Appendix 1. 'IWARF' logic model for summary). A brief introductory video shows participants how to use the intervention and to explain the different features. Participants complete the modules that correspond to their needs, at their own pace within ~8 weeks. Up to 3 total interactions between facilitators and participants will be offered to support participants' engagement with the programme via virtual check-ins. These check-in sessions will occur at intervention-beginning, middle and end (facilitated by a Research Assistant or Research Fellow who is trained/supervised by Harding, Stott and Rohrer). Once participants have completed the trial they will be granted ongoing access to the intervention materials.

4.2 Comparison group

Following consent, baseline measure data collection and randomisation, the waiting list control group will receive explicit signposting to TAU participants may already be receiving (e.g., Rare Dementia Support website). This a wait list study where the control group will be given access to the intervention´s online materials after the individuals' last point of data collection.

4.3 Data collection and management

Check-in sessions and qualitative interviews will be conducted over an internet-based service (e.g. Zoom, MS Teams), and check-in documentation forms will be completed in Microsoft Word, on encrypted and password protected UCL laptops. The intervention – 'IWARF' – will be hosted on a WordPress website, with analytics data collected via custom mechanisms to avoid invoking the use of an external third party. Questionnaire data will be collected via UCL's Qualtrics platform.

4.4 Sampling and sample size

A sample size of 118 participants (59 per group) is required to detect a standardised effect size of 0.4 on the primary outcome measure, mental wellbeing, with 90% statistical power at the 5% significance level. This sample size allows for 20% attrition and is based upon an ANCOVA analysis with a R2 of 0.65 between the primary outcome measure, at the 9-week follow up, and the covariates.

4.5 Randomised controlled trial [WS1a]

This is a pragmatic, single-blinded, two-arm randomised controlled trial (with a nested internal pilot). It will evaluate the effectiveness of 'IWARF' in improving overall mental wellbeing and improvements in the secondary outcome measures. Outcome measures will be collected at baseline (T0), ~9 weeks (i.e., ~1 week after the participant's 3rd check-in session) (post-intervention, T1) and 6 months post baseline (follow-up, T2):

4.5.1 Primary outcome measures

Reflecting the intentions of the intervention, the outcome measures assess the promotion of mental wellbeing. There will be one primary outcome measure for the trial, mental wellbeing, which will be measured using the 14-item version of the 14-item Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS; Tennant et al., 2007). The WEMWBS consists of 14 positively

worded items, including positive affect (feelings of optimism, cheerfulness, relaxation), satisfying interpersonal relationships and positive functioning (energy, clear thinking, self-acceptance, personal development, competence and autonomy). Participants rate their agreement with each statement on a 5-point Likert scale, ranging from "none of the time" (1 point) to "all of the time" (5 points). A cumulative score will be obtained by summing the score for each of the 14 items, resulting in a possible range from 14 to 70, with higher scores indicating greater levels of mental wellbeing. The WEMWBS-14 has high test-retest reliability ($r = 0.83$) and high internal consistency (Cronbach's $\alpha = 0.89$).

4.5.2 Secondary outcome measures

1. Generalised Anxiety Disorder-7 (GAD-7; Spitzer et al., 2006) is a widely used 7-item, 4-point Likert scale designed to screen for GAD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2022) criteria. Participants rate how frequently they have experienced various symptoms consistent with GAD (e.g., feeling nervous, not being able to stop or control worrying, trouble relaxing) on a 4-point Likert scale, ranging from "not at all" (0 points) to "nearly every day" (3 points). A cumulative score will be obtained by summing the score for each of the 7 items, resulting in a possible range from 0 to 21, with higher scores indicating more severe anxiety. The GAD-7 has high test-retest reliability ($r = 0.83$) and high internal consistency (Cronbach's $\alpha = 0.92$).

2. Patient Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001) is a widely used 9-item, 4-point Likert scale designed to screen for and measure the severity of depressive symptomatology according to DSM-5 criteria (APA, 2022). Participants rate how frequently they have experienced various symptoms consistent with depression (e.g., little interest or pleasure in doing things, feeling down, depressed, or hopeless, poor appetite or overeating) on a 4-point Likert scale, ranging from "not at all" (0 points) to "nearly every day" (3 points). A cumulative score will be obtained by summing the score for each of the 9 items, resulting in a possible range of 0 to 27, with higher scores indicating more severe depressive symptomatology. The PHQ-9 has high test-retest reliability ($r = 0.84$) and high internal consistency (Cronbach's $\alpha = 0.89$).

3. An adapated version of the Psychological Adaptation to Genetic Information (PAGIS; Read et al., 2005) was used to measure feelings related to genetic risk and predictive testing. The PAGIS is a 26-item Likert scale, comprising of five domains relevant to evaluating psychological adaptation to genetic information. The five subscales are: (1) 'Nonintrusiveness' consisting of 6 items (e.g., "I can't seem to stop myself from thinking about having this gene"); (2) 'Support' consisting of 6 items (e.g., "It's hard for me to talk about having this gene with my relatives"); (3) 'Self-worth' consisting of 4 items (e.g., "Having this gene makes me feel inferior at times"); (4) 'Certainty' consisting of 5 items (e.g., "I understand how I came to have this gene"); (5) 'Self-efficacy' consisting of 4 items (e.g., "If a problem arises because of this gene I will be

able to find a solution"). Participants are asked to rate the degree of agreement/disagreement with each item on a 6-point Likert scale, ranging from 1 (strongly disagree) to 6 (strongly agree). The internal consistency reliability of the total PAGIS was Cronbach's $\alpha = 0.90$, and the subscale reliabilities ranged from Cronbach's $\alpha = 0.77 - 0.87$.

4. The EQ-5D-5L (Herdman et al., 2011) is a well-validated, generic preference-based patient-reported outcome measure that assesses today's health, comprising a descriptive system with 5 dimensions: (1) 'Mobility' (e.g., "I have no problems in walking about"); (2) 'Self-care' (e.g., "I have no problems washing or dressing myself"); (3) 'Usual activities', including work / study / housework / family or leisure activities (e.g., "I have no problems doing my usual activities"); (4) 'Pain/discomfort' (e.g., "I have no pain or discomfort"); and (5) 'Anxiety/ depression' (e.g., "I am not anxious or depressed"). For each dimension participants are asked to rate themselves on how they feel on that particular day on 5 levels varying from no problems (1; e.g., "I have no problems in walking about") to extreme problems/unable (5; e.g., "I am unable to walk about"). Participants are also invited to rate how good/bad their health is on that day using a visual analogue scale (EQ-VAS) ranging from 0 (worst imaginable health) to 100 (best imaginable health). Participants' responses to each of the 5 dimensions provide a health state or profile represented by a 5-digit number (e.g., 12231) corresponding to response categories reported by participants for successive dimensions, beginning with mobility. Health states are scored using a scoring algorithm from a value set derived from valuation tasks typically undertaken with general population samples (Devlin et al., 2020).

5. The ICEpop CAPability measure for Adults (ICECAP-A; Al-Janabi et al., 2012) assesses five capabilities that are important to one's wellbeing. The ICECAP-A consists of 5 dimensions: (1) 'Stability', referring to one's ability to feel settled and secure (e.g., "I am able to feel settled and secure in all areas of my life"); (2) 'Attachment', referring to one's ability to have love, friendship and support (e.g., "I can have a lot of love, friendship and support"); (3) 'Autonomy', referring to one's ability to be independent (e.g., "I am able to be completely independent"); (4) 'Achievement', referring to one's ability to achieve progress in life (e.g., "I can achieve and progress in all aspects of my life"); and (5) 'Enjoyment' referring to one's ability to experience enjoyment and pleasure (e.g., "I can have a lot of enjoyment and pleasure"). A 4-level response scale is applied for each item and respondents are asked to indicate the one that best describes their overall quality of life now. Overall scores range from 0, which represents 'no capability' to 1, which represents 'full capability'. Overall, the evidence suggests adequate content and construct validity of the ICECAP-A and the intra-class correlation reflecting test-retest reliability was considered adequate ($r = 0.72$ for the full measure).

6. The 24-item Multidimensional Psychological Flexibility Inventory (MPFI-24; Grégoire et al., 2020; Rolffs et al., 2018), will be used to measure ACT-based skills, and primarily

psychological flexibility. The MPFI-24 is a shorter version of the original 60-item measure (Rolffs et al., 2018) which was designed to assess 12 key dimensions of the six distinct components of psychological flexibility, one of the key theoretical tenets of Acceptance and Commitment Therapy (ACT; Hayes et al., 2013), also known as the Hexaflex. The six components of psychological flexibility include: (1) 'Acceptance', defined as willingness to contact unwanted experiences fully; (2) 'Contact with the Present Moment', conceptualised as being in touch and aware of one's experiences; (3) 'Self as Context' conceptualised as one's ability to keep perspective of oneself within one's experiences; (4) 'Defusion', conceptualised as one's ability to step back from unwanted experiences without getting stuck in them; (5) 'Committed Action', which refers to maintaining behaviours that move toward important aspects of life; and (6) Values, which refers to staying connected to the areas of life that are important thereby giving direction to behaviours. The model also proposes 6 distinct components that make up Psychological Inflexibility – these are: (1) 'Experiential Avoidance', which refers to one's attempts to distance oneself in some way from unwanted experiences; (2) 'Lack of Contact with the Present Moment', referring to not paying attention to one's experiences in any given moment; (3) 'Self as Content', which refers to the tendency to (make judgments about experiences resulting in a narrower view of self; (4) 'Fusion', understood as getting trapped in unwanted internal experiences; (5) 'Inaction', referring to one's inability to behave in a way that is consistent to what is important in life; and (6) Lack of Contact with Values, conceptualised as being disconnected from the areas of life that are most meaningful to oneself. The dimensions of flexibility are viewed as critical to promoting individual health and well-being and are therefore promoted within ACT, whereas the dimensions of inflexibility are conceptualised as key elements associated with psychological distress. The Multidimensional Psychological Flexibility Inventory – 24 (MPFI-24) assesses both psychological flexibility (e.g., "In the last two weeks, I was attentive and aware of my emotions") and psychological inflexibility (e.g., "In the last two weeks, negative feelings often trapped me in inaction"). As mentioned above, this scale was created from the 60-item MPFI and used the item response theory analyses to select the 2 most effective items (i.e., the items offering the highest levels of discriminating information for detecting differences between individuals) of each 5-item subscale. Items are rated by participants on a 6-point scale ranging from 1 = 'Never true' to 6 = 'Always true'. Scores on pairs of items are averaged to represent each of the 12 specific dimensions of psychological flexibility and inflexibility in the Hexaflex model. Responses on the twelve flexibility items (i.e., items 1 to 12) can also be averaged to create a flexibility composite score. Similarly, responses on the 12 inflexibility items (i.e., items 13 to 24) can be averaged to create an inflexibility composite score. The reliability of the MPFI-24 subscales and composites have been assessed and both the subscales and composite scores have demonstrated adequate internal consistency with an average Cronbach's $\alpha = 0.83$ and ranging from 0.71 to 0.92.

7. The Office of National Statitistics (ONS) measure for loneliness will be used. based on their recommendations (ONS, 2018) that loneliness can be more comprehensively measured if both direct and indirect measures are used. Specifically, the ONS proposes to use one scale that has been assessed as valid and reliable (as well as a measure that will allow participants to say for themselves whether they feel lonely, providing further insight into the subjective feeling of loneliness for different people. The ONS proposes four items to capture different aspects of loneliness; the first three items are from the UCLA 3-item loneliness scale, a very widely used scale with evidence of good reliability and validity (Hughes et al., 2004) (Item 1: "How often do you feel that lack of companionship?"; Item 2: "How often do you feel left out?"; Item 3: "How often do you feel isolated from others?") using a 3-point rating scale (Hardly ever or never, some of the time, Often). The fourth item is a direct question about how often participants feel lonely (Item 4: "How often do you feel lonely?") using a 5-point rating scale (Often/always, Some of the time, Occasionally, Hardly ever, Never).
8. Health and social care resource use, including primary care, outpatient appointments , as well as impacts on productivity and other personal costs, will be measured with a participant reported resource use measure (AR-RUM) which has been co-developed with people living at-risk of fFTD/FAD and healthcare professional stakeholders.

Table 1. Schedule to list recruitment, consent and which measures are collected at different timepoints.

Questionnaire	Screening	BL	9 weeks	6 months
Participant information sheet and consent to provide screening responses	X			
Eligibility check (screening responses)	X			
Online opt-in consent process		X		
Demographics		X		
WEMWBS		X	X	X
GAD-7		X	X	X
PHQ-9		X	X	X
PAGIS		X	X	X
EQ-5D-5L		X	X	X
ICECAP-A		X	X	X
MPFI-24		X	X	X

ONS loneliness measure (UCLA 3 item plus subjective question)	X	X	X
AR-RUM	X	X	X
SUS		X *[for intervention group only]*	

4.5.3 Data collection

The primary mode of data collection for all the outcome measures will be technology mediated (see Figure 3). The check-in sessions and qualitative interviews (process evaluation only) will be conducted via an internet-based service (e.g. Zoom, MS Teams) or telephone platform by a member of the research team. The questionnaire outcome measures will be collected via the UCL online Qualtrics survey platform and then uploaded onto the UCL secure Data Safe Haven data management platform by a member of the research team. Check-in session documentation forms will be completed digitally during the check-in sessions by the researcher and uploaded onto the UCL secure Data Safe Haven data management platform by a research team member. Analytics will be collected via the intervention web-based platform using a custom analytics dashboard built into the website and resulting data will be uploaded to the UCL Data Safe Haven by a member of the research team. Assessments will be done at baseline (T0), ~9 weeks after baseline (T1), and 6 months after baseline (follow-up, T2). Demographic data will be collected at baseline (e.g., age, gender, ethnicity, genetic risk status, education, occupation).

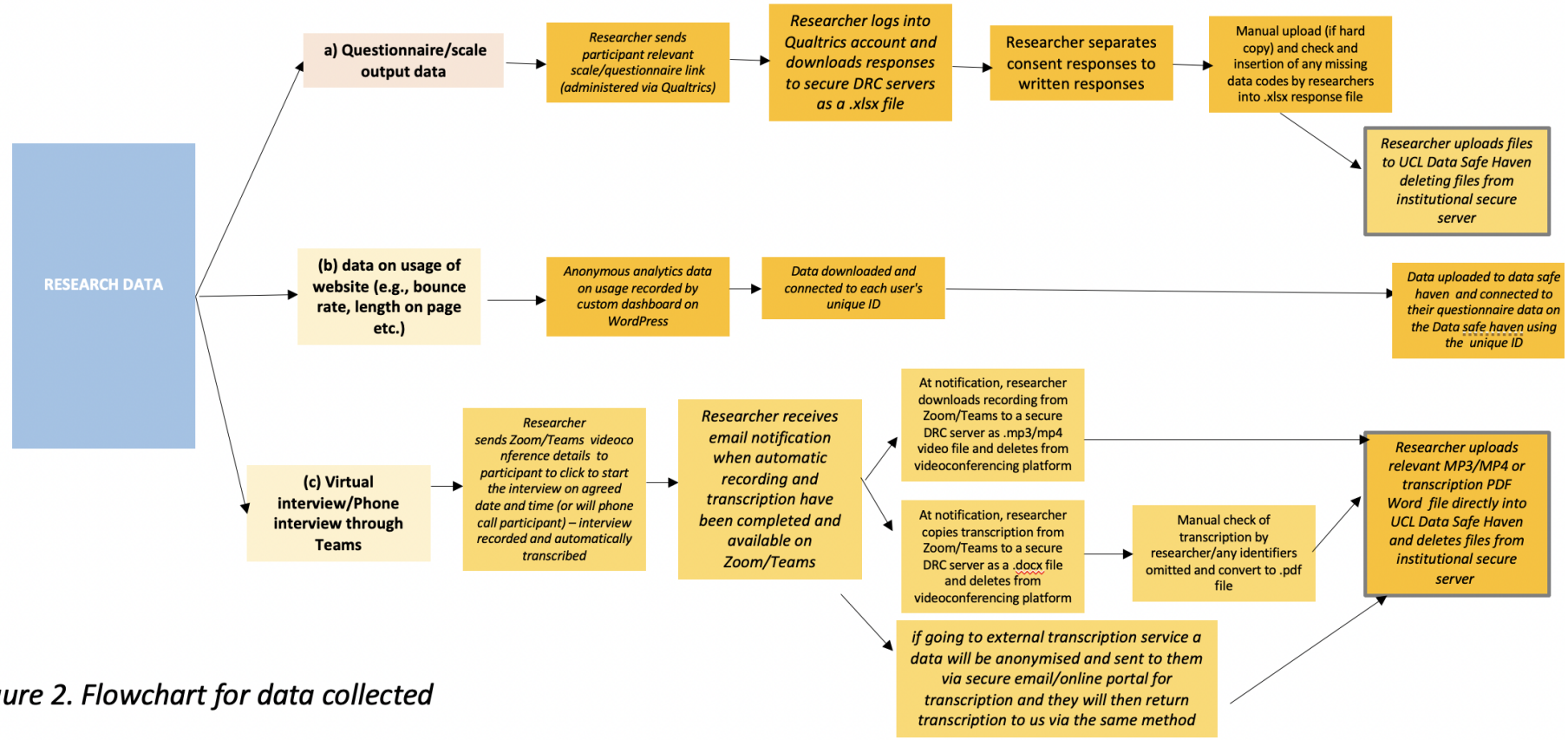


Figure 2. Flowchart for data collected

collection pathways and data management stipulations

Whilst every effort will be made to follow-up participants as close as possible to the defined time points this may vary e.g. due to the different speeds at which participants choose to move through the intervention.. Date of data collection will be recorded.

4.5.4 Data analysis

Primary analysis will be conducted on an Intention To Treat (ITT) basis, blinded to treatment allocation. The primary assessment for effectiveness of the intervention will be adjusted estimates of the scores on the WEMWBS (14 item) scale between the intervention and Treatment As Usual (TAU) groups assessed at the 9-week follow up.

A linear mixed effects model adjusting for baseline scores, and other stratification variables (i.e., diagnosis, at-risk group type and gender) will be fitted for the scores on the WEMWBS at both the 9 weeks and 6 months follow ups. Similar models will be fitted for all the continuous secondary outcomes. All estimates of effect will be presented together with 95% confidence intervals. A sensitivity analysis will be conducted to assess the impact of the number of times the intervention is accessed

The aim is to minimise missing data; however, predictors of missingness will be investigated using regression models and any predictors found will be considered for inclusion in the models. Multiple imputation will be employed to address missing scores where appropriate. Analysis of complete case data will be completed as a sensitivity analysis to establish the sensitivity of the treatment effect estimates to the missing data.

A Statistical Analysis Plan (SAP) will be written and signed off before completion of data collection. The independent committees (i.e., TSC & DMEC) will have the opportunity to comment on the SAP. If any deviations from the planned statistical analyses are required these will be documented in the end of trial statistical analysis reports

4.6 Internal pilot study [WS1b]

4.6.1. Internal pilot outcomes

- Progression criteria will be measured at 9 months (full study is 30 months from first participant recruited, with a projected recruitment of ~3-6 participants per month (in the first 24 months).
- 'Stop' [stop the trial], 'Review '[with adaptation to trial process], 'Go' [without adaptation] criteria thresholds are based on levels allowing completion of the trial within 30 months.

4.6.1. Internal pilot criteria:

1. Recruitment ('Stop'/'Review'/'Go' based on modelling non-linear recruitment scenarios):
    - Go=30 participants recruited
    - Review=15+ recruited
    - Stop=<15 recruited

2. Intervention attendance (i.e. check-in videoconference sessions):
    - Go=70%+ videoconference sessions attended
    - Review=60-69% attended
    - Stop=<60% attended

3. Intervention attendance (i.e. the number of participants who have logged in and used the system more than once):
    - Go=60%+ online content accessed
    - Review=40-59% online content accessed
    - Stop=<40% online content accessed

We will have limited data on retention and primary outcome completion at 9 months but will keep under continuous review. In relation to these, we will only stop the trial after the pilot if there is no outcome data or no one is retained at 9 months.

4.7 Process evaluation [WS2]

The process evaluation will run alongside the trial and will apply mixed-methods (quantitative questionnaires (e.g. the SUS), semi-structured interviews, and analysis of data from the online platform). It will be conducted in line with established guidance frameworks (Moore et al., 2015; O'Cathain et al., 2019). It will examine throughout the intervention period how participants engage with and adhere to particular aspects of 'IWARF' (e.g. most/least frequently visited pages, the most 'popular' modules/sessions).

Change mechanisms will be investigated by exploring the barriers, facilitators and contextual factors which influence the uptake and implementation of 'IWARF' (e.g. the at-risk genetic status of participants). The extent to which 'IWARF' may have changed behaviours beyond the intervention (e.g. mindfulness practice, values-guided action) will be explored. The usability of the website will be evaluated with the System Usability Scale (SUS; Brooke, 1996).

4.7.1 Quantitative data collection (N = 59)

A System Usability Scale (SUS) will be administered to the IWARF intervention group immediately post-intervention as part of their Qualtrics battery of outcome measures. This 10-item scale will quantitatively evaluate the overall usability of the 'IWARF' platform. Each item is a statement (e.g. "I thought 'IWARF' was easy to use") and responses given on a 5-point Likert scale 0 (strongly agree) to 4 (strongly disagree). Total scores range from 0 to 40 which are then converted to 0-100 and normalised to produce a percentile ranking. The SUS is easy to administer, reliable and valid and effectively differentiates between usable and unusable systems. We will also collect data from the online platform regarding usability (e.g. frequency and length of use, which modules/ activities / pages users most frequently visit;

average length of time spent on each module / lesson / page per user; from tablet or PC). The number of contacts with the facilitator will also be recorded.

4.7.2 Qualitative data collection

Semi-structured interviews will be undertaken using an internet-based service (e.g. Zoom, MS Teams) or telephone, with a sub-sample of the intervention participants. These will be recorded and professionally transcribed. The topic guides will be guided by the process evaluation parameters described in recognised frameworks (Moore et al., 2015; O'Cathain et al., 2019) and drawing upon theoretical models such as Normalisation Process Theory (NPT; Murray et al., 2010) They will be developed in partnership with the PPI group and our collaborators. Regular meetings will be held with the research team to identify any new questions which arise from emerging themes. The content of any contact with the facilitator between check-in sessions will also be recorded (e.g. questions about the intervention, any requests for troubleshooting).

4.8 Health Economics

Health and social care resource use, including primary care, outpatient appointments, support groups as well as impacts on productivity and activities of daily living, will be measured with a participant reported resource use measure that has been developed for this population. An internal pilot will be conducted to assess the feasibility and acceptability of the resource use measure in the first 2 to 3 months of the trial (assessing to the first 15 participants responses). If completion rates indicate the resource use measure is not acceptable, edits will be made at this point and the IWARF PPI group will be asked for feedback on items where changes have been made.

Resource use will be translated into costs using published unit costs for the cost year for the evaluation (NHS reference costs (https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/), PSSRU (Jones et al., 2023), BNF (https://www.nice.org.uk/bnf-uk-only)). Development costs, staff inputs, material and equipment associated with the IWARF intervention will be elicited from structured interviews with the trial team, finance staff and clinical sites as required.

Data will be summarized by mean and SD if data are normal, or median and IQR if data are skewed. The economic analyses will include the intent to treat population as for the statistical analysis. Data will be assessed for missingness, and if the assumption of missing at random can be made, then multiple imputation will be used if the number of cases lost due to incomplete information exceeds 10%. Imputed datasets will be combined using Rubin's rules before undertaking analyses. Sensitivity analyses will be performed to examine departures from the missing at random assumption in the imputation models.

A within-trial health economic analysis will be conducted based on the trial follow- up period of 6 months. Patient pathways will be developed with input from the research team given the limited published evidence available for this population. Net incremental costs and outcomes

will be computed using the area under the curve method. Costs and outcomes will not be discounted as the within-trial time horizon is less than 12 months. A range of health economic analyses will be presented to inform comprehensive assessment of cost-effectiveness for decision makers. The primary analysis will be a cost-utility analysis. The net monetary benefit will be used to summarise QALY benefits against willingness to pay thresholds (NICE, 2013). Sufficient capability will be assessed using the ICECAP-A, which is a broader wellbeing/capability measure, cost-effectiveness will be assess against the threshold for a year of sufficient capability well-being (Kinghorn and Afentou 2021). A cost-effectiveness analysis estimating the incremental costs of achieving clinically significant improvement in at-risk mental wellbeing as this analysis will be relevant to health care professionals, healthcare decision makers and service users; however, interpretation of this ICER will be limited as there is no threshold to determine what represents good value for money A range of sensitivity analyses will be conducted to address the impact of uncertainty on our findings.

The base case analysis will be conducted from a societal perspective including impact on ability to work, a further analysis with a UK NHS and personal social services perspective will be conducted to allow comparison with other published economic evaluations.

A health economic analysis plan will be written following good practice with reporting of the health economic analysis conforming to the Consolidated Health Economic Evaluation Reporting Standards (Husereau et al., 2022).

5. ASSESSMENT OF SAFETY

5.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in either a trial study participant which does not necessarily have a causal relationship with the intervention.

Serious Adverse Event (SAE): Any adverse event that a) Results in death; (b) Is life threatening; (c) Requires hospitalisation or prolongation of existing hospitalisation; (d) Results in persistent or significant disability or incapacity; or (e) Is otherwise considered medically significant by the investigator. Pre-existing conditions do not qualify as adverse events unless they worsen over the course of the trial.

5.2 Collecting, recording and reporting of adverse events

Assessment of AEs and SAEs brought to the attention of the research team will be undertaken and overseen by an independent Data Monitoring & Ethics Committee (DMEC), who will report to the Trial Steering Committee (TSC). The DMEC will be able to advise on changes to the conduct of the trial via recommendations to the TSC and will also receive regular safety reports from the team.

The adverse event reporting period for the trial begins as soon as participants consent to take part and one month after their final data collection ends. All adverse event data the research team are made aware of will be collected and recorded in line with University College London's Research Ethics Committee stipulations on Adverse Event Reporting – Serious and Non-Serious (as outlined in the approval letter dated 10/01/2024). Reporting of SAEs will also form part of the trial delegation log and be covered in training for research team members

involved in data collection. The documentation for SAE and AE reporting is outlined in the trial folder on the Data Safe Haven.

Reports will be sent to the Trial Management Team, the Research Ethics Committee, DMEC and TSC within the required timelines from the approval letter (immediately upon notification of an SAE, and within ten days of the AE being brought to the research team's attention). Other adverse events will be noted in the same log as the SAEs and a monthly report will be compiled by the Trial Lead (EH) for review by the Trial Management Team.

Safety analysis will be pre-specified analyses in the statistical plan led by NWORTH and can be represented graphically e.g. as volcano plots or in the usual tabular format. The former plots all SAEs and provides a visual representation of outliers. This method is preferred to inferential analysis, as they would be under-powered. Using graphical methods will allow the DMEC to identify any potential safety signals and these will be reported to the TSC.

A copy of the AE and SAE CRF will be stored at the recruiting site in the ISF, and those signed by the Chief Investigator stored in the Trial Master File (TMF).

Given the nature of the intervention, we do not feel there are serious safety concerns for the participants. However, we will be collecting data on psychological distress (e.g. anxiety and depression). This data will be available to the DMEC during the course of the trial.

If someone living at-risk of a familial dementia becomes symptomatic with dementia during the course of the intervention, we will discuss with them on a case by case basis regarding continuing with the trial (e.g. completing measures, accessing the intervention). Participants are always able to withdraw at any point for any reason and will be reminded of this. We will ensure we record their change in health status in the relevant trial documentation (e.g. a file note) and it has been confirmed by our trial statistician that this change in status will pose no issue for analysis.

6. PROJECT MANAGEMENT

The study is sponsored by University College London (UCL) and the governance and management of the study will be undertaken by UCL. There are several parties involved in project management: UCL (study governance and data collection); NWORTH (randomization, trial analysis) and Swansea (health economics analysis). Study-specific SOPs will be developed as required and will be addressed throughout the study period and regularly reviewed. Best practice will be employed throughout to ensure the trial is managed to the highest possible standard. Appropriate supervision and training of research staff and training in Good Clinical Practice (GCP) will be ensured.

We have established an independent Trial Steering Committee (TSC), an independent Data Monitoring & Ethics Committee (DMEC) and a Trial Management Group (TMG). The TSC and DMEC will meet at agreed time intervals, which will be documented in the committees' terms of reference or charter. Both will consist of an independent chair and an independent statistician. The DMEC will be able to advise on changes to the conduct of the trial via recommendations to the TSC and will also receive regular safety reports from the TMG.

6.1 Trial Steering Committee

The project's TSC will oversee the running of the study on behalf of the sponsor and funder and will have overall responsibility for the continuation or termination of the trial. It will ensure that the trial is conducted in accordance with the principles of GCP and the relevant regulations, and provide advice on all aspects of the study.

6.2 Independent Data Monitoring Committee

The project's DMEC will monitor the data and ethics aspects of the study and provide advice on changes to the conduct of the trial via recommendations to the TSC.

6.3 Trial Management Group

A TMG will oversee the day-to-day running of the trial and is composed of research team members, including the Chief Investigators, Trial Lead, Programme Manager and Statistician (see Co-I table at the top of this document). In addition, the group may include other members of the trial team with specific expertise, such as PPI Co-Leads and Health Economists. The TMG will meet frequently during set up and subsequently on an agreed periodic basis once the trial is open to recruitment, and will monitor all aspects of conduct and progress, and ensure the protocol is adhered to.

6.4. Patient and public involvement (PPI)

Our PPI members will be involved throughout the duration of the study. PPI Co-Leads Nikki Zimmermann and Valerie Mansfield will support RDS member involvement with the study. All public-facing documents have been developed following DRC templates established with input from PPI colleagues and RDS members to ensure they are user-friendly and suitable for all levels of literacy skills. The current version of the intervention (which has undergone feasibility testing) has been co-created with input from individuals living at-risk of a familial form of dementia. Additional modules will also be co-created in consultation with EBE.

PPI colleagues and RDS members will be invited to be involved in discussions throughout the trial (e.g., about the development of interview questions for the process evaluation, the interpretation of the research results and the production of a plain English summary and plans for the dissemination of the study findings). The trial team will develop and deliver short and simple research methods sessions if required, e.g. 'what is a randomised controlled trial?' to help colleagues understand this specific research process.

7. ETHICS & REGULATORY APPROVALS

This study has been approved by the UCL Research Ethics Committee (Project ID/Title: 8545/008: Improving wellbeing in at-risk familial dementias (IWARF).

7.1 Psychological distress protocol

The study protocol, associated documentation, and all substantial amendments thereof will be submitted for review by UCL Research Ethics Committee (REC). The main ethical concern for the trial is the potential for psychological distress. As part of this study we are inviting people living at-risk of inheriting a form of dementia to engage with exercises which relate to their experience of this and to respond to questions about their experience interacting with an intervention which aims to provide support for this. In doing so, there is a risk that

participants could become distressed when particular topics arise in the modules/questionnaires (e.g. survivors' guilt for individuals who have tested negative for inheriting the gene, who may have a sibling who has tested gene-positive and will inherit the dementia). We have a protocol in place in a situation whereby a participant becomes distressed about an aspect of a research visit or intervention. This protocol ensures all researchers are able to follow standardised procedure. The steps being taken to reduce and manage these risks is outlined in the following protocol, detailed below, and included within UCL-REC-approved documents relating to this study. This protocol ensures all researchers can follow standardised procedure.

The protocol is outlined as follows:

(i) This project is supervised by Dr Emma Harding and Prof Joshua Stott, both of whom are experienced research psychologists with counselling and clinical psychologist qualifications and extensive experience working with this population. The researchers within the project will report to either of the named supervisors' where expressions of emotional distress are conveyed by participants over Zoom/Teams/phone interviews, email communication or responses to questions in surveys. An email trigger will be set up via Qualtrics to alert a member of the research staff to any non-negative answer to the final item of the PHQ-9 (about suicidality), and/or if severe anxiety or depression are indicated. We will also incorporate signposting to mental health services in the end page of the Qualtrics survey, and a member of the research team will send a follow up via email to the participant within 72 hours of receiving the notification. Research team members will document any indications of psychological distress and any follow up action recommended and taken following discussion with senior members of the team. For the process evaluation qualitative interviews, research team members administering the interviews will complete a post-interview form following each interview which will confirm and detail the presence/absence of any cause for concern or incidence of distress.

(ii) Every report of participant distress will be pro-actively discussed by the research team members collecting/analysing data with Dr Harding, Prof Stott and/or Dr Brotherhood on a case by case basis but in general, the steps that follow will apply: if distress is conveyed over email or in a survey response, the participant will be contacted to remind them that participation in the study is voluntary and that they can withdraw at any time and that there is no obligation to respond to any questions that make them upset and will be offered an opportunity to debrief as well as linked to further support resources as appropriate. If distress is conveyed over Zoom/MS Teams/phone interviews, the researcher will offer the participant a break or reschedule for another time and will also remind the participant of their right to withdraw from the study at any time without need to justify why, offer an opportunity to debrief, and signpost to any further support resources as appropriate. Research team members will document any indications of

psychological distress and any follow up action recommended and taken following discussion with senior members of the team.

(iii) In case of controls who may feel disappointed for having been allocated to the control group, the researcher will explain the value of the control group in randomised controlled trials, that this is a methodological requirement. Will also remind the participant that this is a wait-list study and the intervention will become available for them as soon as we finish data collection.

7.2 Reward and recognition for participants

All participants enrolled in the trial will receive a £15 voucher for a range of online shops as a gesture of appreciation for their contribution to research.

8. DATA MONITORING

8.1 Quality Assurance (QA) and Quality Control (QC) of data

QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with the principles of GCP and applicable regulatory requirements.

QC is the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the research-related activities are fulfilled.

8.2 Monitoring plan

A Monitoring Plan will be prepared prior to participant recruitment detailing the monitoring strategy for the trial. The plan will include requirements for day-to-day centralised monitoring.

8.3 Confidentiality

All data will be handled in accordance with General Data Protection Regulation (2018). A pseudonymised version of the datasets will be made available in line with our funder requirements. Audiovisual recordings containing personal identifiers will be substituted for pseudo names during transcription. The transcription service will be a UCL-approved third party.

All trial staff and members of the research team will preserve the confidentiality of participants taking part in the trial, and the Sponsor is registered as a Data Controller with the Information Commissioners Office. The only exception to this would be in the event of a safeguarding whereby the researchers observe or hear anything that causes very serious concern about the participant's health, safety or well-being, or that of another person. If this happens, the researchers have a duty to inform an appropriate professional and will contact

the lead investigator of this study in the first instance. This has been explicitly outlined in the Participant Information Sheets.

9. DATA HANDLING

Electronic data collected will be downloaded from respective platforms (e.g., Qualtrics, Zoom/Teams) to secure UCL servers and uploaded to the UCL Data Safe Haven. The Data Safe Haven has been certified to the ISO27001 information security standard and conforms to NHS Digital's Data Security and Protection Toolkit. Built using a walled garden approach, where the data is stored, processed and managed within the security of the system, avoiding the complexity of assured endpoint encryption. A file transfer mechanism enables information to be transferred into the walled garden simply and securely.

Researchers will complete UCL Data Safe Haven training, including learning how to securely upload scanned/electronic data from their research sites onto the repository. Personal details (e.g., participant name and contact details) will be available on the Data Safe Haven, alongside a unique participant identifier.

10. PATHWAYS TO IMPACT

From project inception, we have used NHS-England's framework for stakeholder analysis to identify key audiences to communicate and engage with (all of whom we have strong existing networks and collaborations with). They include but are not limited to:

- NHS staff and services (through co-applicants [e.g., Fox, Rohrer] and clinical investigator panel co- chairs (collaborators Mummery/Warren are senior NHS consultants leading national clinical services).
- Commissioners (e.g., one of the collaborators, Dr Mummery, sits on several national commissioning bodies as well as the National Neuroscience Advisory Group - a collaboration of professional bodies, patients, policy, and commissioning leads [see letter of support]).
- Policy makers (e.g., All Party Parliamentary Group on dementia (APPG), The Late Baroness Sally Greengross).
- National mental health guideline developers (e.g., Centre for Outcomes Research and Effectiveness/National Collaborating Centre for Mental Health).
- Third sector organisations (through established partnerships, committee positions, etc, e.g., FTD UK, International FTD Association, OneDementiaVoice, CADR (enrich-Cymru), Centre for Innovation in Aging (age-Cymru), The Awen Institute.
- Psychological workforce training (Stott is acting joint programme director of the UK's largest clinical psychology training course [160 trainees]; his department is the biggest psychology workforce training provider in the UK [480 trainees]).

At a minimum we will also disseminate via:

- Conference presentations and papers.
- Co-applicants' Twitter channels (collectively >8000 followers).
- Blogs.
- Podcasts.

- Our three costed-for public stakeholder events.
- Open access webinars.
- TV/radio/newspaper interviews (extensive team experience of communicating dementia research through 'mainstream' media e.g., https://www.youtube.com/watch?v=7Qmu0MLHoGU).
- Local and trade press.
- The National Brain Appeal-funded 15 annual newsletters and RDS meetings provided to ~5500 RDS members.

11. INDEMNITY

Cover for harm as a result of the design or conduct of the study has been arranged with the study Sponsor (aligned with UCL Insurance provided for research studies: https://ethics.grad.ucl.ac.uk/uclinsurance.php).

12. FINANCIAL ASPECTS

This study is funded by the National Institute for Health & Care Research (NIHR) and will be managed in accordance with the relevant policies and procedures.

13. DEFINITION OF END OF STUDY

This is defined as the date of the last assessment of the last participant.

14. ARCHIVING

UCL recognise that there is an obligation to archive study-related documents at the end of the study (as such end as defined within this protocol). The Chief Investigator confirms that this project´s researchers will archive the study master file at UCL in line with all relevant legal and statutory requirements. In line with our funder requirements (see in line with UCL's rules around data retention: https://www.ucl.ac.uk/library/collections/records-office/records-retention/retention-schedule/research-data), we are required to de-identify the data and make this available re-use free of charge, as open data, safeguarded data or controlled data. The access category data is classified as should be selected to minimise the risk of disclosing personal information. This must be deposited within an NIHR-approved data repository 3 months after the grant end date.

The data will be stored at the Dementia Research Centre, UCL. Long-term data archiving will be managed in line with UCL's records office policy.

15. REFERENCES

Al-Janabi, H., Flynn, T. N., & Coast, J. (2012). Development of a self-report measure of capability wellbeing for adults: The ICECAP-A. *Quality of Life Research*, *21*(1), 167–176. https://doi.org/10.1007/S11136-011-9927-2/FIGURES/3

American Psychiatric Association. (2022). *Diagnostic and statistical manual of mental disorders (5th edition)*.

Brooke J. (1996). SUS: A 'quick and dirty' usability scale. In *SUS: Usability Evaluation in Industry* (pp. 189–194). Taylor Francis.

Craig, P., Dieppe, P., Macintyre, S., Mitchie, S., Nazareth, I., & Petticrew, M. (2008). Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*, *337*(7676), 979–983. https://doi.org/10.1136/BMJ.A1655

Devenney, E. M., Ahmed, R. M., Halliday, G., Piguet, O., Kiernan, M. C., & Hodges, J. R. (2018). Psychiatric disorders in C9orf72 kindreds study of 1,414 family members. *Neurology*, *91*(16), E1498–E1507. https://doi.org/10.1212/WNL.0000000000006344

Devlin, N., Parkin, D., & Janssen, B. (2020). *Methods for analysing and reporting EQ-5D data*. Springer Nature.

Garc ıa-Toro, M., ıa Cruz Sánchez-G omez, M., ıa Madrigal Zapata, L., & Javier Lopera, F. (2020). "In the flesh": Narratives of family caregivers at risk of Early-onset Familial Alzheimer's Disease. *Dementia*, *19*(5), 1474–1491. https://doi.org/10.1177/1471301218801501

Grégoire, S., Gagnon, J., Lachance, L., Shankland, R., Dionne, F., Kotsou, I., Monestès, J. L., Rolffs, J. L., & Rogge, R. D. (2020). Validation of the english and french versions of the multidimensional psychological flexibility inventory short form (MPFI-24). *Journal of Contextual Behavioral Science*, *18*, 99–110. https://doi.org/10.1016/J.JCBS.2020.06.004

Harding, E., Greaves, C., Goldsmoth-Sumner, A., Hayes, O., Rossi-Harries, S., Zimmermann, N., Tsipa, A., Rohrer, J., Brotherhood, E., & Stott, J. (2024). *Improving wellbeing in at-risk familial frontotemporal dementia (IWARF): a feasibility study of a blended digital/human online intervention* .

Hayes, S. C., Levin, M. E., Plumb-Vilardaga, J., Villatte, J. L., & Pistorello, J. (2013). Acceptance and Commitment Therapy and Contextual Behavioral Science: Examining the Progress of a Distinctive Model of Behavioral and Cognitive Therapy. *Behavior Therapy*, *44*(2), 180–198. https://doi.org/10.1016/J.BETH.2009.08.002

Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., Bonsel, G., & Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research*, *20*(10), 1727–1736. https://doi.org/10.1007/S11136-011-9903-X/TABLES/5

Husereau, D., Drummond, M., Augustovski, F., de Bekker-Grob, E., Briggs, A. H., Carswell, C., Caulley, L., Chaiyakunapruk, N., Greenberg, D., Loder, E., Mauskopf, J., Mullins, C. D., Petrou, S., Pwu, R. F., & Staniszewska, S. (2022). Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *Https://Doi.Org/10.1177/23814683211061097*, *7*(1). https://doi.org/10.1177/23814683211061097

Jones, K. C., Weatherly, H., Birch, S., Castelli, A., Chalkley, M., Dargan, A., Forder, J. E., Gao, M., Hinde, S., Markham, S., Ogunleye, D., Premji, S., & Roland, D. (2023). *Unit costs of health and social care 2022 manual.*

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. *Journal of General Internal Medicine*, *16*(9), 606–613. https://doi.org/10.1046/J.1525-1497.2001.016009606.X

Lewit-Mendes, M. F., Lowe, G. C., Lewis, S., Corben, L. A., & Delatycki, M. B. (2018). Young People Living at Risk of Huntington's Disease: The Lived Experience. *Journal of Huntington's Disease*, *7*(4), 391–402. https://doi.org/10.3233/JHD-180308

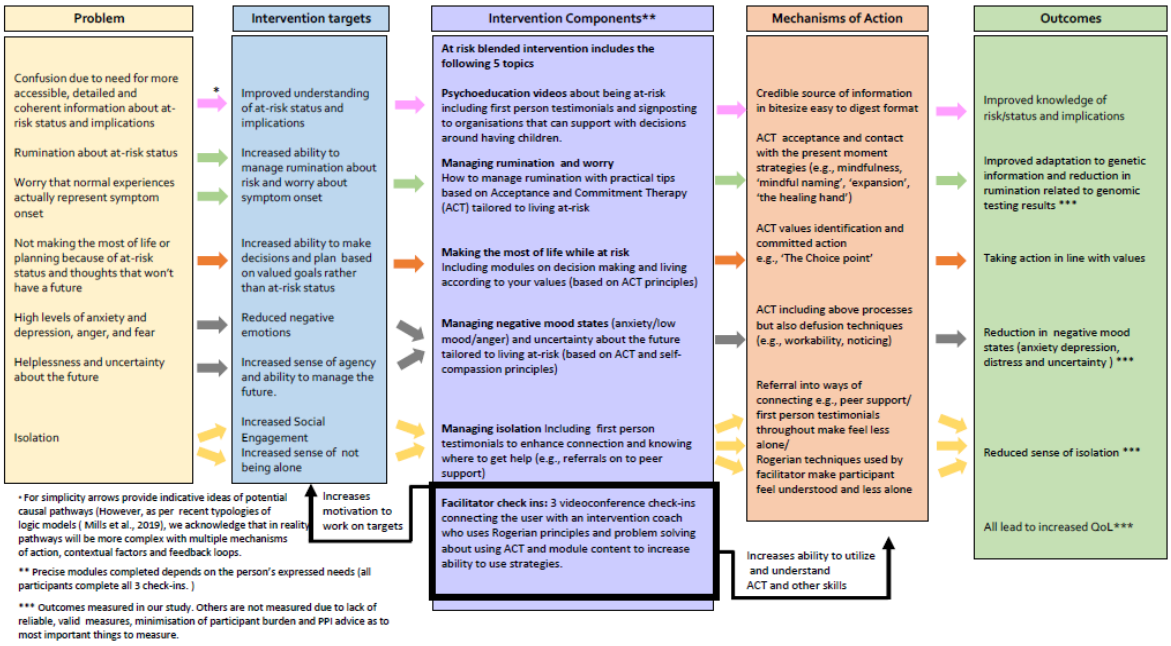
Moore, G. F., Audrey, S., Barker, M., Bond, L., Bonell, C., Hardeman, W., Moore, L., O'Cathain, A., Tinati, T., Wight, D., & Baird, J. (2015). Process evaluation of complex interventions: Medical Research Council guidance. *BMJ*, *350*. https://doi.org/10.1136/BMJ.H1258

Murray, E., Treweek, S., Pope, C., MacFarlane, A., Ballini, L., Dowrick, C., Finch, T., Kennedy, A., Mair, F., O'Donnell, C., Ong, B. N., Rapley, T., Rogers, A., & May, C. (2010). Normalisation process theory: A framework for developing, evaluating and implementing complex interventions. *BMC Medicine*, *8*(1), 1–11. https://doi.org/10.1186/1741-7015-8-63/TABLES/3

NICE. (2013). *Guide to methods of technology appraisal*.
O'Cathain, A., Croot, L., Duncan, E., Rousseau, N., Sworn, K., Turner, K. M., Yardley, L., & Hoddinott, P. (2019). Guidance on how to develop complex interventions to improve health and healthcare. *BMJ Open*, *9*(8), e029954. https://doi.org/10.1136/BMJOPEN-2019-029954
Office of National Statistics. (2018). *Measuring loneliness: guidance for use of the national indicators on surveys*.
Read, C. Y., Perry, D. J., & Duffy, M. E. (2005). Design and Psychometric Evaluation of the Psychological Adaptation to Genetic Information Scale. *Journal of Nursing Scholarship*, *37*(3), 203–208. https://doi.org/10.1111/J.1547-5069.2005.00036.X
Rolffs, J. L., Rogge, R. D., & Wilson, K. G. (2018). Disentangling Components of Flexibility via the Hexaflex Model: Development and Validation of the Multidimensional Psychological Flexibility Inventory (MPFI). *Assessment*, *25*(4), 458–482. https://doi.org/10.1177/1073191116645905/ASSET/IMAGES/LARGE/10.1177_1073191116645905-FIG2.JPEG
Russell, D., Hoare, Z. S. J., Whitaker, R., Whitaker, C. J., & Russell, I. T. (2011). Generalized method for adaptive randomization in clinical trials. *Statistics in Medicine*, *30*(9), 922–934. https://doi.org/10.1002/SIM.4175
Russell, D., Peplau, L. A., & Cutrona, C. E. (1980). The revised UCLA Loneliness Scale: Concurrent and discriminant validity evidence. *Journal of Personality and Social Psychology*, *39*(3), 472–480. https://doi.org/10.1037/0022-3514.39.3.472
Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Löwe, B. (2006). A Brief Measure for Assessing Generalized Anxiety Disorder. *Archives of Internal Medicine*, *166*(10), 1092. https://doi.org/10.1001/archinte.166.10.1092
Tennant, R., Hiller, L., Fishwick, R., Platt, S., Joseph, S., Weich, S., Parkinson, J., Secker, J., & Stewart-Brown, S. (2007). The Warwick-Dinburgh mental well-being scale (WEMWBS): Development and UK validation. *Health and Quality of Life Outcomes*, *5*(1), 1–13. https://doi.org/10.1186/1477-7525-5-63/TABLES/4

16. APPENDICES

Appendix 1: 'IWARF' logic model


Problem
Intervention targets
Intervention Components**
Mechanisms of Action
Outcomes
Confusion due to need for more accessible, detailed and coherent information about at-risk status and implications
Rumination about at-risk status
Worry that normal experiences actually represent symptom onset
Not making the most of life or planning because of at-risk status and thoughts that won't have a future
High levels of anxiety and depression, anger, and fear
Helplessness and uncertainty about the future
Isolation
*
Improved understanding of at-risk status and implications
Increased ability to manage rumination about risk and worry about symptom onset
Increased ability to make decisions and plan based on valued goals rather than at-risk status
Reduced negative emotions
Increased sense of agency and ability to manage the future.
Increased Social Engagement
Increased sense of not being alone
At risk blended intervention includes the following 5 topics
Psychoeducation videos about being at-risk including first person testimonials and signposting to organisations that can support with decisions around having children.
Managing rumination and worry
How to manage rumination with practical tips based on Acceptance and Commitment Therapy (ACT) tailored to living at-risk
Making the most of life while at risk
Including modules on decision making and living according to your values (based on ACT principles)
Managing negative mood states (anxiety/low mood/anger) and uncertainty about the future tailored to living at-risk (based on ACT and self-compassion principles)
Managing isolation Including first person testimonials to enhance connection and knowing where to get help (e.g., referrals on to peer support)
Facilitator check ins: 3 videoconference check-ins connecting the user with an intervention coach who uses Rogerian principles and problem solving about using ACT and module content to increase ability to use strategies.
Credible source of information in bitesize easy to digest format
ACT acceptance and contact with the present moment strategies (e.g., mindfulness, 'mindful naming', 'expansion', 'the healing hand')
ACT values identification and committed action e.g., 'The Choice point'
ACT including above processes but also defusion techniques (e.g., workability, noticing)
Referral into ways of connecting e.g., peer support/ first person testimonials throughout make feel less alone/
Rogerian techniques used by facilitator make participant feel understood and less alone
Improved knowledge of risk/status and implications
Improved adaptation to genetic information and reduction in rumination related to genomic testing results ***
Taking action in line with values
Reduction in negative mood states (anxiety depression, distress and uncertainty) ***
Reduced sense of isolation ***
All lead to increased QoL***
Increases motivation to work on targets
Increases ability to utilize and understand ACT and other skills
• For simplicity arrows provide indicative ideas of potential causal pathways (However, as per recent typologies of logic models (Mills et al., 2019), we acknowledge that in reality pathways will be more complex with multiple mechanisms of action, contextual factors and feedback loops.
** Precise modules completed depends on the person's expressed needs (all participants complete all 3 check-ins.)
*** Outcomes measured in our study. Others are not measured due to lack of reliable, valid measures, minimisation of participant burden and PPI advice as to most important things to measure.