Acceptability and Feasibility of a Brief, Multi-Component Acceptance and Commitment Therapy (ACT) Intervention to Support Those Living At Risk of Inherited Prion Diseases

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Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

Name: Rhianna Brien

Date: 12/06/2025

Overview

Inherited forms of prion disease follow an autosomal dominant inheritance pattern, meaning those with an affected parent have a 50% risk of developing the condition. This poses distinct and prolonged psychological challenges, often beginning well before symptom onset. Despite this, the needs of at-risk individuals are under-researched and specialist psychological support is limited. This thesis, presented in three parts, aims to address these gaps.

Part One presents a systematic scoping review of 24 studies exploring the psychological experience of living at risk for autosomal dominant neurological conditions. Findings highlight how emotional responses to genetic risk are shaped by personal, relational, and systemic factors and fluctuate across the life course, often intensifying during key life transitions. The review identifies a need for longitudinal research to clarify when support is most needed, as well as a clear gap in evidence on what interventions might be most effective. Recommendations for future research and methodological limitations are discussed.

Part Two evaluates the feasibility and acceptability of a brief, multi-component Acceptance and Commitment Therapy (ACT) intervention tailored for individuals at risk of inherited prion disease. Predefined progression criteria for recruitment, retention, completion, data completeness, and acceptability were all met. Qualitative feedback indicated the workshop was relevant and useful, though individual preferences varied around timing and content. Findings support progression to a randomised controlled trial and offer key insights for future development, with recommendations for flexible approaches to eligibility, timing, and delivery.

Part Three offers a critical reflection on the research process, considering planning, methodological challenges, researcher development and the challenges surrounding facilitation.

Impact Statement

This thesis contributes to the limited literature on rare, genetic neurodegenerative conditions, laying a foundation for future research and the development of tailored psychological support for at-risk populations.

It offers one of the first detailed investigations into the psychological experience of living at risk for autosomal dominant neurological conditions, synthesising existing qualitative and quantitative evidence to highlight specific challenges and identify points across the life course when support may be most needed. It also demonstrates the feasibility and acceptability of a novel, brief, multi-component Acceptance and Commitment Therapy (ACT) intervention tailored to individuals at risk of inherited prion disease (IPD), providing groundwork for a future randomised controlled trial. This approach offers a flexible, resource-efficient model of care which is particularly valuable within NHS services, where long-term psychological support may not always be viable

To the author's knowledge, this is the first psychological intervention trialled in an IPD at-risk population, with broader implications for both research and clinical practice. It contributes to the growing evidence base for single-session ACT and highlights the potential for such interventions in other rare or underserved conditions, where traditional models of support may not be feasible. These interventions could also foster intergenerational resilience by equipping individuals with coping strategies that extend beyond the individual to benefit families and future generations. While focused on IPD, the findings also speak more broadly to the psychological needs of individuals at risk for other genetic neurodegenerative conditions such as Huntington's disease, familial frontotemporal dementia, and familial Alzheimer's disease. Insights may further extend to individuals at risk of acquired prion diseases who similarly face prolonged uncertainty in the absence of clear care pathways.

Clinically, this research provides practical insights that will directly inform service development at the National Prion Clinic. The findings also provide important context for professionals – including genetic counsellors, psychologists, nurses, and neurologists – helping them offer more sensitive, informed care, and emphasising the need not to overlook untested individuals or the longer-term challenges of living with genetic risk.

Dissemination is underway, with plans for peer-reviewed publication, academic conference presentations, and collaboration with patient organisations. Public engagement efforts – including presentations to staff and service users at the National Prion Clinic Open Day and the CJD Support Network annual family support meeting – aim to raise awareness, reduce stigma, and humanise the experience of those living at risk.

This research lays the groundwork for sustained academic, clinical, and societal impact on how IPD is understood and supported both now and in the future.

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Part 1: Literature Review

The Psychological Experience of Living at Risk of an Autosomal Dominant Neurological Condition in Adulthood: A Scoping Review

Abstract

Aims: While the psychological impact of genetic testing for autosomal dominant neurological conditions (ADNCs) is well documented, less is known about the broader experience of living at risk, particularly for rarer, understudied conditions. This scoping review aims to map the existing literature, synthesise evidence on the psychological experience of at-risk individuals, and identify key gaps to inform future research and support. **Method:** Following Joanna Briggs Institute and PRISMA-ScR guidelines, a systematic search of PsycINFO, MEDLINE, and Web of Science (November 2024) identified studies exploring the psychological experience of adults (≥18 years) at risk for ADNCs. There were no restrictions on publication date or study design. **Results:** 24 studies, published between 1990 and 2024 , met inclusion criteria. Studies show that emotional responses to genetic risk are dynamic and shaped by personal, relational, and systemic factors. Psychological distress often intensifies during major life transitions such as family planning, witnessing a relative's decline, or entering new relationships. Key themes included identity disruption, anticipatory grief, and coping through living fully and maintaining hope. However, the literature is limited by small, homogenous samples, an overreliance on qualitative designs, and inconsistent reporting of psychological outcomes. No longitudinal studies were identified, and only a small number of studies investigated interventions tailored to this population. **Conclusions:** This is the first review to systematically synthesise evidence on this topic. It underscores the fluctuating nature of psychological distress across the life course and highlights critical gaps in knowledge and care. Future research should prioritise longitudinal approaches and consider the use of control or comparison groups to better assess intervention effectiveness.

Introduction

Autosomal dominant neurological conditions (ADNCs) are hereditary disorders affecting the brain and nervous system, caused by a single mutated gene on one of the 22 non-sex chromosomes (autosomes). This mutated gene can be inherited from either parent, with each affected individual having a 50% chance of passing it on to their offspring (Simpson, 1984). ADNCs encompass a broad range of disorders, including Huntington's disease (HD), familial Alzheimer's disease (FAD), genetic frontotemporal dementia (FTD), spinocerebellar ataxias (SCAs), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and inherited prion diseases.

Symptoms for most ADNCs typically manifest in adulthood, although some individuals experience earlier (juvenile) onset (Chabriat et al., 2009; Klockgether et al., 2019; Mead, 2006; Roos, 2010). While clinical presentations vary, ADNCs are generally characterized by progressive neurological degeneration, which can lead to motor symptoms, cognitive decline, and neuropsychiatric disturbances (Chabriat et al., 2009; Dion et al., 2009; Greaves & Rohrer, 2019; Klockgether et al., 2019; Mead, 2006; Roos, 2010). ADNCs are typically progressive and fatal, with no cure and limited disease-modifying treatments available; therefore, treatment focuses primarily on symptom management (Chabriat et al., 2009; Dion et al., 2009; Greaves & Rohrer, 2019; Klockgether et al., 2019; McColgan & Tabrizi, 2018).

Beyond physical decline, ADNCs have profound psychological and social consequences for affected individuals and their families (Klockgether et al., 2019; Roos, 2010; Silva et al., 2020). This often begins long before symptom onset, as the hereditary nature of ADNCs means many individuals experience the diagnosis of a parent or close family member before developing the condition themselves (van der Meer et al., 2014).

Psychological Implications of Living at Risk of Autosomal Dominant Neurological Conditions

Advances in predictive genetic testing have transformed understanding of ADNCs, allowing individuals to learn their genetic status before developing symptoms (Goldman, 2020). Substantial research has examined the impact of receiving a gene-positive result, with findings generally suggesting that most individuals adapt well over time and that severe psychological outcomes are rare (Crook et al., 2017; Crozier et al., 2015; Gargiulo et al., 2009; Hagberg et al., 2011; Howard et al., 2025; Paulsen et al., 2013; Schwartz et al., 2019). Studies also highlight the complexity surrounding testing decision-making, citing concerns such as the emotional burden of knowing and a perceived lack of benefit in the absence of treatment (Mendes et al., 2019; Crook et al., 2021).

Far fewer studies have investigated the psychological consequences of living at risk for an ADNC outside of the testing context. Among those that have, findings are inconsistent – some report significant psychological burden, while others find no clear association with poorer mental wellbeing (Chisholm et al., 2013; Schwartz et al., 2019; Sobregrau et al., 2022). Nevertheless, there is growing recognition that the uncertainty of potential disease onset can pose unique psychological challenges, including stigma, anticipatory grief, and disruptions in employment, relationships, and family planning (Bombard et al., 2009; Hartzfeld et al., 2015; Mendes et al., 2021; van der Zwaan et al., 2022). These challenges can exist regardless of whether someone has tested positive for a pathogenic mutation or remains untested but has a family history placing them at risk (Schwartz et al., 2019). For the purposes of this review, “at risk” will therefore be used to describe both groups: asymptomatic individuals who are gene positive and asymptomatic individuals who remain untested.

The limited research on the overall experience of living at risk raises concerns about how this population is conceptualised and represented in the literature. The dominant focus on testing outcomes may reflect a reductionist view, overlooking the broader psychosocial context in which individuals make sense of risk over time. Findings from such studies may also lack generalisability, as those who decide to get tested may be more able to cope with an unfavourable result, while individuals experiencing greater distress are more likely to be lost to follow-up (Goldman, 2020; Tibben, 2007). Additionally, the perspectives of untested individuals – who comprise a substantial portion of those at risk – remain underrepresented in such studies (Baldwin et al., 2024; Crook et al., 2017; Crozier et al., 2015; Greaves & Rohrer, 2019).

There is a need to better understand the psychological evidence base relating to individuals at risk for ADNCs. Some recent reviews have begun to address this gap. A scoping review by Mahmood et al. (2022) synthesised qualitative findings on the lived experience of HD. Emotional themes such as loneliness, uncertainty, hope, and processes of adaptation and acceptance were identified. However, this review focused exclusively on qualitative designs, included symptomatic individuals as well those at risk, and excluded untested at-risk individuals – limiting its applicability to the specific psychological experience of living at risk. Similarly, van Lonkhuizen et al. (2023) systematically reviewed health-related quality of life (QoL) in pre-manifest and manifest HD, concluding that tested at-risk individuals report similar QoL to controls, according to most studies. However, untested individuals were again excluded and the focus was on QoL across all disease stages rather than broader psychological experience for those at risk. To the author's knowledge, no reviews have systematically mapped the psychological literature on at-risk populations across ADNCs and methodological approaches.

Given the rarity of many ADNCs and the resulting small, heterogeneous evidence bases,

synthesising findings across conditions may provide a more comprehensive picture of shared psychological challenges and unmet needs, particularly as evidence suggests different genetic conditions share many common emotional effects (McAllister et al., 2007). Such knowledge may guide the development of support and interventions beyond the point of testing which has been identified as a priority, particularly for those who remain untested (Mahmood et al., 2022; Zarotti et al., 2020). This is important as at-risk individuals likely have minimal or no engagement with healthcare services due to being asymptomatic which may result in their needs being overlooked.

Research Aims and Objectives

The aim of this scoping review is to systematically map the literature on the psychological experiences of adults living at risk for ADNCs and identify common themes, gaps, and conceptual frameworks. This approach is well suited to synthesising a broad and methodologically diverse evidence base in a relatively under-explored area (Arksey & O'Malley, 2005). Specifically, the review will address the following questions:

1. What evidence is available regarding the psychological experiences of adults living at risk for an ADNC? Specifically, what study designs and methods have been used?
2. What is currently known about these experiences, and what factors influence them?
3. What gaps remain in our understanding of the psychological experience of living at risk for an ADNC?

Method

The current review was conducted in accordance with the methodological guidance of the Joanna Briggs Institute (JBI) and the PRISMA Extension for Scoping Reviews (PRISMA-ScR) statement and checklist (Peters et al., 2020; Tricco et al., 2018). A protocol was developed and pre-registered on the Open Science Framework in November 2024 (OSF: https://osf.io/xzpgv].

A quality assessment of the included sources was not conducted as scoping reviews primarily aim to map key concepts and available evidence rather than assess study quality (Peters et al., 2022; Pollock et al., 2023). Methodological and clinical limitations were noted where possible.

Eligibility Criteria

The Population, Concept, Context (PCC) framework was used to guide the search strategy and eligibility criteria, as detailed in Appendix A (Peters et al., 2020; Pollock et al., 2023).

Studies were included if they focused on adults (≥18 years) at risk for an ADNC, defined as asymptomatic individuals who either tested positive for a pathogenic mutation or had a known family history but had not undergone testing. Eligible studies had to examine the psychological experience of living at risk as a primary aim or central research question. In studies involving mixed populations, data needed to be reported separately for at-risk individuals to allow meaningful extraction and synthesis.

Only peer-reviewed journal articles published in English were included, with no restrictions on study design or publication date. Studies were excluded if they did not provide separable data for relevant conditions, focused primarily on the psychological aspects of genetic testing (a topic already extensively studied), or examined psychological changes solely as potential preclinical manifestations rather than as aspects of lived experience. Non-peer-reviewed publications, systematic reviews, commentaries, and studies not published in full were also excluded. Reference lists of relevant reviews were screened, but no additional eligible studies were identified.

Information Sources

Searches were conducted across three major electronic databases by the lead author during the third week of November 2024 with no start date restriction: PsycINFO (APA), MEDLINE (Ovid), and Web of Science Core Collection (Clarivate). Full search terms and

retrieval results were systematically documented for transparency. Backward and forward citation searches were conducted to identify additional relevant studies. Grey literature was not searched due to the focus on peer-reviewed journal articles to ensure rigor and consistency in the included studies.

Search Strategy

A comprehensive search strategy was developed in collaboration with a health sciences librarian, based on the PCC framework and following PRISMA-ScR guidelines (Pollock et al., 2023; Tricco et al., 2018). To ensure broad retrieval, the search included a comprehensive list of ADNCs determined in consultation with a consultant neurologist specialising in genetic neurological conditions and informed by *Neurology: A Queen Square Textbook* (Howard et al., 2024). This list was combined with terms related to the autosomal dominant nature of these conditions such as "genetic," "inherited," "familial," and psychological concepts such as "psych*," "experience," and "self-identity". Boolean operators, truncation, and controlled vocabulary were employed to maximize sensitivity and precision. The full search strategy, including all keywords and database-specific controlled vocabulary terms, is presented in Appendix B.

The search strategy was piloted in MEDLINE and PsycINFO to assess effectiveness and refined using the PRESS (Peer Review of Electronic Search Strategies) framework to improve accuracy and completeness (McGowan et al., 2016).

Study Selection

References were imported into EndNote for duplicate removal, and Rayyan software was used to manage and document screening decisions. Two reviewers (RB and EC) independently screened all records at both the title/abstract and full-text stages.

At title and abstract screening, interrater agreement was 97.7%, with a Cohen's Kappa of 0.80. For full-text screening, agreement was 92.1%, with a Kappa of 0.84. These values

indicate substantial to almost perfect interrater reliability (Landis & Koch, 1977). Discrepancies were resolved through discussion. A third reviewer was available to arbitrate unresolved disagreements but was not required.

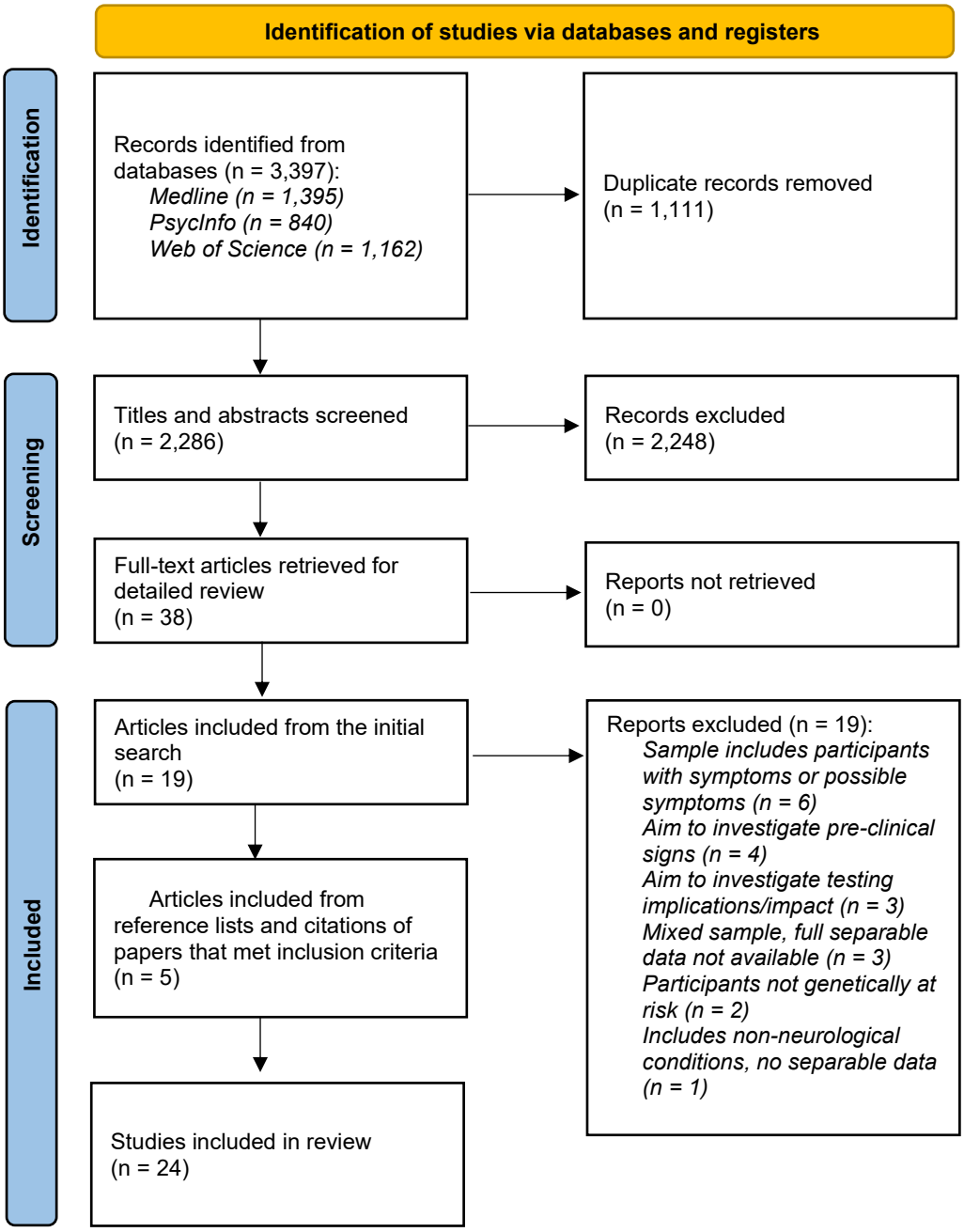
Data Extraction and Synthesis

Data extraction was carried out by the lead author (RB) using a predefined standardised form to ensure consistency (see Appendix C). The form was developed based on previous scoping reviews and refined with input from the research team to ensure all relevant study details were captured.

Findings were synthesised using a narrative synthesis approach, with a thematic framework used to organise and interpret key psychological concepts emerging across studies. Given the broad scope and heterogeneity of included studies, thematic categorisation was supported by basic numerical analysis of study characteristics to aid interpretation and transparency.

Figure 1

PRISMA flow diagram (Page et al., 2021)



Results

Study Selection and Characteristics

The database searches retrieved a total of 3,397 records. After removing duplicates and limiting to English-language publications, 2,286 records were screened by title and abstract. 38 full-text articles were assessed for eligibility, with 19 excluded for not meeting inclusion criteria. 19 met the criteria and were included in the review. An additional five were identified through reference and citation searching, resulting in a final total of 24 studies (see Figure 1 for PRISMA flow diagram).

Table 1 summarises study characteristics, and Figure 2 provides a visual overview of the findings. Included studies were published between 1990 and 2024, with nearly half (n = 11, 46%) published in the past five years. Studies were conducted across nine countries, most commonly the United States (n = 6) and the United Kingdom (n = 5). Sample sizes varied widely, ranging from 10 to 4,171 participants (median = 33). Nearly one-third (29%) included fewer than 20 participants, and 63% fewer than 50. Most studies (92%) focused on a single ADNC, with HD the most frequently studied condition by far (n = 15, 63%).

Study Designs

Of the 24 included studies, 12 (50%) used qualitative designs, eight (33%) were quantitative observational, and four (17%) employed mixed methods. One-third of the total studies (n = 8) included comparison groups; these varied between disease stage comparisons (such as comparing at-risk individuals to symptomatic individuals) and comparisons with clinical or general population controls. The remaining studies used mixed samples, often including partners, other family members not at risk, or tested-negative relatives. While these studies collected data separately for different subgroups, they did not perform subgroup analyses. Nine of the included studies focused exclusively on individuals at risk.

Focus and Outcomes

Qualitative studies mainly explored the lived experience of being at risk, addressing broad themes such as wellbeing, identity, and coping. Two qualitative studies had a more specific focus: one examined caregiving and another perceptions of stigma and discrimination. Quantitative studies primarily assessed psychological outcomes, with depression (n = 5), quality of life (n = 4), general mental health (n = 4), anxiety (n = 3), coping (n = 3), and life satisfaction (n = 3) the most commonly measured. Less frequently studied outcomes included suicidal ideation, childhood adversity, and attachment (each n = 1). Five studies evaluated the feasibility or acceptability of psychological interventions, employing qualitative (n = 1), quantitative cross-sectional (n = 1), and mixed methods (n = 3) designs.

Table 1

Key Characteristics of Included Studies

Qualitative Studies						
Author(s), Year, Country	**Aim**	**N***	**Population**	**At risk sample age/gender**	**Methodological Features**	**Main Findings**
Boutte, M.I. (1990), United States	To explore the meaning of being 'at risk'.	20 (20)	MJD: ***Untested (n = 20)***	Not reported	Semi-structured interviews exploring lived experience of risk.	Risk perception shaped by resemblance to affected relative; salience fluctuates.
Cooper, H. et al. (2024), United Kingdom	To explore the experience of maintaining psychological well-being while at risk.	12 (12)	HD: ***Untested (n = 12)***	Mean age 40.5 (SD 13.93), range 19-66; 9F, 3M	Semi-structured interviews investigating wellbeing and coping.	Themes suggest managing wellbeing is a dynamic challenge requiring active, multifaceted coping.
Dratch, L. et al. (2024), United States	To understand risk perception & broader experiences of risk.	14 (14)	FTD & ALS: ***Gene+ (n = 14)***	Mean age 44 (SD 9.6) range 31-63; 10F, 4M	Semi-structured interviews exploring lived experience and risk perception.	Identity threat and uncertainty prominent; salience varied over time & among individuals.
Eccles, F. J. R. et al. (2021), United Kingdom	To investigate experiences of a mindfulness-based cognitive therapy course.	17 (11)	HD: ***Gene+ (n = 11);*** Supporters (n = 6)	Age range 24–64, mean and SD not specified; 7F, 4M	Semi-structured interviews to assess participant experiences of a mindfulness-based cognitive therapy course.	Participants found the course beneficial, reporting reductions in psychological distress & better emotion regulation.

Etchegary, H. (2009), Canada	To explore how people cope with genetic illness using a stress and coping framework.	24 (11)	HD: ***Gene+ (n = 3)***; ***Untested (n = 6)***; ***Pre-results (n = 2)*** Gene-/Int-G (n = 7); Manifest (n = 2); Family (n = 4)	Full sample: Mean age 46 (SD 11.3) range 21-73; 18F, 6M	Semi-structured interviews exploring coping strategies.	At risk groups most likely to engage in secondary control coping (e.g., rationalization, social support).
Etchegary, H. (2011), Canada	To explore how people live with increased risk and the biographical disruption it evokes.	24 (11)	Shared sample with Etchegary (2009).	Shared sample with Etchegary (2009).	Semi-structured interviews investigating lived experience	Risk not always salient, influenced by life stage & family history. Most adopt a pragmatic approach.
Garcia-Toro, M. et al. (2020), Colombia	To explore the experiences of family caregivers with genetic risk.	27 (27)	Early-onset FAD: ***At risk (n = 27)***	Mean age 35 (SD 12.2), range 18-60; 26F, 1M	Semi-structured interviews exploring caregiving experiences.	Both burdens & benefits described: adds to fear of future, while also enhancing disease understanding
Ho & Hocaoglu (2011), United Kingdom	To investigate how HD affects the experience of everyday life & what issues are on patients' minds.	31 (3)	HD: ***Gene+ (n = 3);*** Stage 1 (n = 5); Stage 2 (n = 5); Stage 3 (n = 3); Stage 4 (n = 9); Stage 5 (n = 6)	Full sample: Age range 30-89, mean/SD not reported; 21F, 10M	Semi-structured interviews & seven classified themes to distinguish frequency.	At-risk individuals mostly reported social issues (e.g. lack of support). Emotional issues also prominent (e.g. anxiety regarding family)

Howard, J. et al. (2024), United Kingdom	To explore the experience of living with genetic risk.	35 (20)	MND: ***Gene+ (n = 6); Untested (n = 14);*** Gene- (n = 4); Manifest (n = 11)	Age range 24–69, mean/SD not reported; 12F, 7M, 1withheld	Intensive interviews exploring lived experience and coping mechanisms.	Fluctuating salience of risk influenced by context. Living fully and health-promoting behaviours are key.
Quaid, K.A. et al. (2008), United States	To explore the everyday experience of being at risk	37 (37)	HD: ***Untested (n = 37)***	Mean age 43 (SD 7.6), range not reported; 25F; 12M	Unstructured open-ended interviews exploring lived experience.	Risk disclosure is an ongoing, context-dependent process influenced by relationships & employment. Hope is a crucial factor.
Wauters & Hoyweghen. (2022), Belgium	To explore fears of genetic discrimination & coping strategies in individuals at risk.	12 (11)	HD: ***Gene+ (n = 7); Untested (n =4);*** Gene- (n = 1)	Full sample: Mean age 41 (SD not reported), range 28–60; 10F, 2M	Semi-structured interviews exploring perceptions of stigma and discrimination.	Fears of direct & subtle genetic discrimination, influenced by family experiences. Some persist in patterns of secrecy, others opt for transparency.
Wieringa, G. et al. (2022), United Kingdom	To explore the experience of 10 individuals with pre-manifest HD.	10 (10)	HD: ***Gene+ (n = 10)***	Mean age 38 (SD not reported) range 25-50; 7F, 3M	Semi-structured interviews exploring lived experience and individual meaning.	Three themes were reported: ‘feeling limited by time’, ‘the perception of stalling time’ & ‘making the most of time’

Quantitative Studies						
A'Campo, L. et al. (2012), The Netherlands	To evaluate the feasibility of the Patient Education Program for HD (PEP-HD) in premanifest and manifest HD	101 (19)	HD: ***Gene+ (n = 19);*** Partners (n = 14); Manifest (n = 40); Caregivers (n = 28)	Mean age 41.3 (SD 10.4), range not reported; 13F, 6M	Single-group pilot study measuring feasibility. Outcomes: depression & anxiety (HADS), quality of life (SF-36), coping (UCL) & psychosocial burden (BELA-P-k).	Those at risk & their partners improved coping by seeking social support more often. No improvement in psychological outcomes.
Bergman, M. et al. (2017), Sweden	To explore overall & domain-specific life satisfaction & sense of coherence (SOC) in relation to biopsychosocial variables.	49 (49)	FAD: ***Untested (n = 49)***	Median age 50 (SD not specified), range 21-83; 19F, 30M	Cross-sectional study investigating life satisfaction (LISAT-11) and sense of coherence (SOC-13).	High life satisfaction; stronger SOC linked to better psychological health & associated with being male & beyond expected age of onset.
Bilal, H.et al. (2023), Australia	To investigate whether HD psychosocial stressors are related to depression symptoms.	57 (33)	HD: ***Gene+ (n = 33);*** Manifest (n = 24)	Mean age 44.3 (SD 10.8), range 29–65; 24F, 9M	Cross-sectional study investigating depression (Neuro-QoL) & HD stressors.	Stress regarding the future had strongest association with depression symptoms for those at risk.

Cecchin, C. et al. (2007), Brazil	To determine the depression scores of MJD patients, spouses, individuals at risk & MS control group & to evaluate if correlation with motor disability.	246 (80)	MJD: ***At risk (n = 80);*** Manifest (n = 79); Spouses (n = 43) Comparison: MS controls (n =44)	Mean age 30.5 (SD 9.7), range not specified; 60F, 20M	Cross-sectional comparative study investigating depression symptoms (BDI) & degree of motor disability (BI) (if symptomatic).	Most scores within normal range for those at risk. Moderate to severe symptoms of depression found in only 6.3%.
Chisholm, L. et al. (2013), United States	To determine & compare psychological well-being among symptomatic, prodromal, at risk & healthy controls.	228 (65)	HD: ***Untested (n = 65);*** Prodromal (n = 37); Manifest (n = 31) Comparison: Controls (n = 95)	Mean age 46.9 (SD 13.9), range not specified; 42F, 23M	Cross-sectional comparative study - stress (PSS), mood (PANAS), life satisfaction (SWLS), depression (BDI) & QoL (Global QOL).	Psychological health comparable to controls. At-risk individuals reported higher positive affect.
Paulsen et al. (2005), United States	To examine suicidal ideation in individuals at risk for and diagnosed with HD.	4171 (712)	HD: **At risk (n = 712);** Minor soft signs (n = 363); Early Motor Symptoms (n = 408); Manifest (n = 2688)	Mean age 38.9 (SD ll.0), range not specified; 412F, 300M	Cross-sectional study investigating frequency of suicidal ideation using disease-specific scale (UHDRS).	Frequency of suicidal ideation doubled from 9.1% in at-risk persons with a normal neurological examination to 19.8% in at-risk persons with soft signs.

Swearer, J.M. et al. (2001), United States	To assess psychological symptoms in those at risk, patients with mild FAD, head injury patients, patients with clinical depression & controls.	77 (17)	Early-onset FAD: ***Untested (n = 17)*** Comparison: Mild FAD (n = 6) Head injury (n = 16); Depressed (n = 10); Control (n = 28)	Mean age 47.9 (SD 4.9), range 42-58; 9F, 8M	Cross-sectional comparative study investigating psychological symptoms (SCL-90-R).	No sig differences in depression or anxiety from controls; though nearly half reported distress at some point, often linked to onset of family member.
van der Meer, L. et al. (2014), The Netherlands	To investigate childhood experiences & psychological characteristics in offspring of a parent with genetic disease compared with partners.	293 (96)	HD: ***Pre-test (n = 74)*** CADASIL: ***Pre-test (n = 13)*** HCHWA-D: ***Pre-test (n = 9)*** Comparison: HBOC (n = 70) Partners (n = 127)	HD: Mean age 34.1 (SD 10.1), range 18-63; 38F, 36M. CADASIL: Mean age 35.7 (SD 11.6), range 20-56; 4F, 9M HCHWA-D: Mean age 37.4 (SD 9.2), range 27-55; 5F, 4M	Cross-sectional comparative study investigating adverse childhood experiences (NLES), attachment (ECR-R), mental health (MHI-5), psychological symptoms (BSI).	Neurogenetic offspring had higher attachment anxiety, more adverse childhood experiences & poorer mental health.

Mixed-methods Studies

Axelman, K. et al (2003), Sweden	To investigate the psychosocial consequences of being at different risk for AD, compared with population sample.	551 (106)	FAD: ***Untested (n = 106);*** "Low risk" (n = 37) Comparison: Population sample (n = 408)	Mean age 56 (SD 11.7), range not reported; 57F, 43M	Cross-sectional comparative study investigating coping (JCS), life satisfaction (LSQ-SF) & attitudes to risk (survey).	"High-risk group" assessed quality of personal relationships & everyday life higher than population sample, but nearly 90% felt anxiety about risk.
Gluyas, C. et al. (2023), Australia	To identify support needs of individuals at risk & evaluate psychoeducation forums.	103 (83)	HD: ***Gene+ (n = 83);*** Significant others (n = 20)	Not reported	Phase one: researcher-developed survey to assess support needs Phase two: evaluated acceptability of forum using feedback questionnaire.	Forums addressing emotional challenges & future planning were well-received. Participants valued peer connection & practical strategies. Attendance high.
Poos, J. et al. (2022), The Netherlands	To assess an online mindfulness-based stress reduction (MBSR) course for anxiety & depression.	13 (13)	FTD: ***Gene+ (n = 7); Untested (n = 6)***	Mean age 52.3 (SD 11.7), range 29-67; 8F, 5M	Single-group pilot study assessing acceptability (evaluation form/ FFMQ) & feasibility. Outcomes: depression & anxiety (HADS), symptoms (SCL-90-R), coping (UCL-19), QoL (SF-36), stress (PSS).	MBSR significantly reduced anxiety & depression. Participants found the course beneficial, indicating it could be feasible for those at risk.

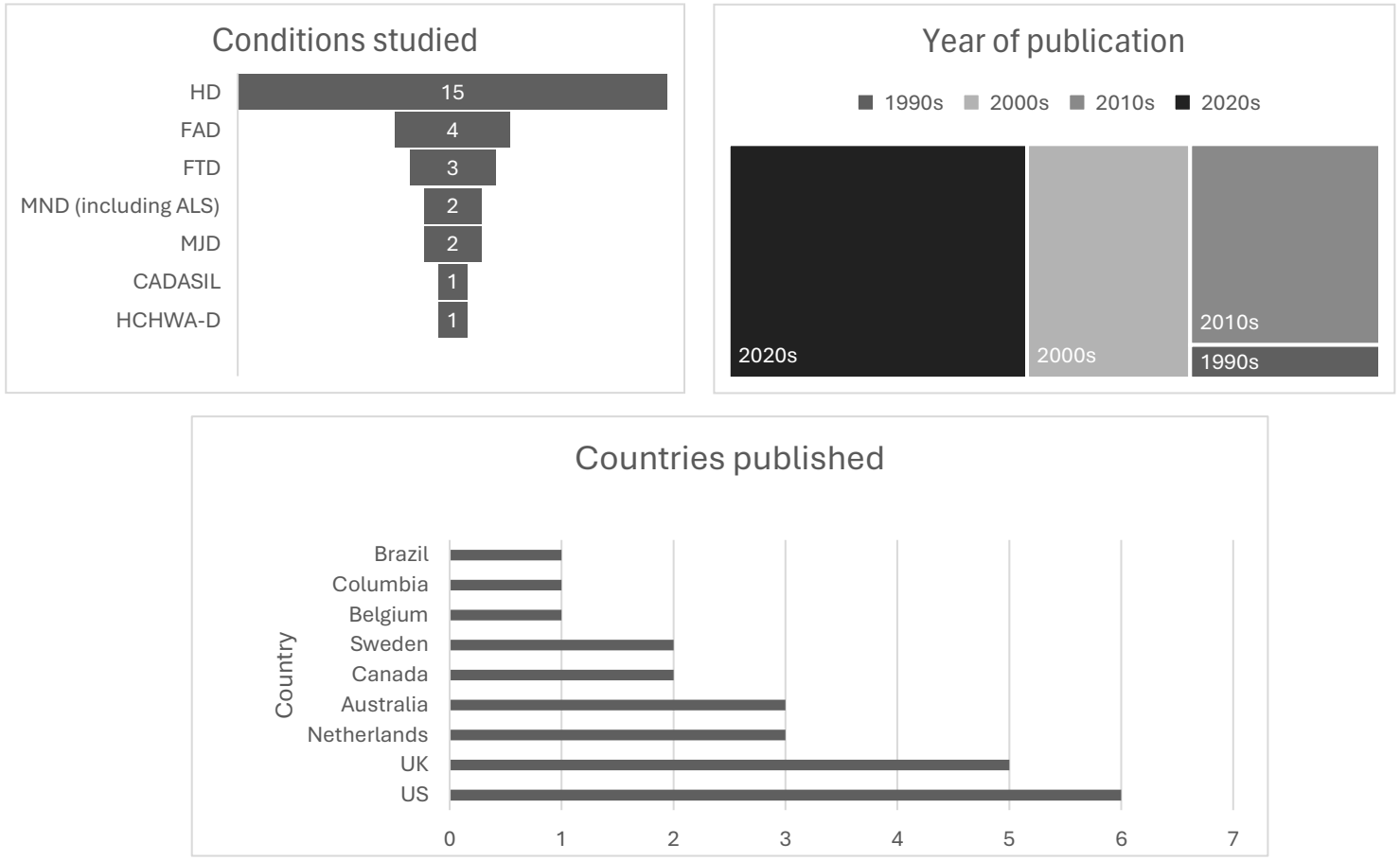
Velissaris, S. et al. (2023), Australia	To evaluate the feasibility & impact of an 8-week MBSR program.	10 (10)	HD: ***Gene+ (n = 10)***	Mean age 49 (SD not reported), range 36–60; 5F, 5M	Single-group pilot study investigating acceptability (interviews) & feasibility. Outcomes: mindfulness skills (FFMQ) & psychological adjustment (HADS/PWI)	MBSR is feasible & well-accepted with high retention & completion rates. Participants valued peer support & reported fewer HD ruminations. Mood scores in "normal" range at all time points.

Note. Italicised bolded groups indicate the primary at-risk sample. Semicolons separate additional groups where applicable. "N" indicates total sample size, with the at-risk group in parentheses. "Comparison" refers to any control or comparison group(s). Demographic characteristics (e.g., age, gender) are reported for the at-risk group where available; otherwise, full-sample data are shown.

Risk status abbreviations: Gene+ = gene positive; Untested = has not undergone predictive testing; At risk = risk status acknowledged but testing status not specified (may include both untested and gene+ individuals) Gene− = gene negative; Int-G = intermediate gene result; Pre-test = awaiting test results
Condition abbreviations: HD = Huntington's Disease; FAD = Familial Alzheimer's Disease; FTD = Frontotemporal Dementia; MJD = Machado-Joseph Disease; MND = Motor Neuron Disease; ALS = Amyotrophic Lateral Sclerosis; CADASIL = Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; HCHWA-D = Hereditary Cerebral Hemorrhage with Amyloidosis–Dutch type.
Other abbreviations: F = female; M = male.

Figure 2

Visual Overview of Study Characteristics



Note. The figure displays conditions studied (top left) countries where studies were published (right) and publication decades (bottom left).

Sample Characteristics

Participant characteristics are summarised in Table 1. Only age and gender are included in the table, as other demographic variables were reported too inconsistently across studies to allow meaningful comparison.

Across the included studies, 6,138 unique participants were represented. Of these, 1,459 were participants at risk, comprising 23% (n = 336) who were untested, 14% (n = 206) who were gene-positive, and 7% (n = 98) who were pre-test or awaiting results. For the remaining 56% of at-risk participants, testing status was not specified. These totals account for overlapping samples, as two studies used data from the same cohort (Etchegary, 2009, 2011).

Most studies reported age (79%) and gender (75%) for at-risk participants, with women slightly overrepresented (60%). Mean ages ranged from 30.5 to 56, with participants spanning from 18 to 83 years. Reporting of other demographic characteristics – such as ethnicity (n = 10), education (n = 9), relationship status (n = 9), and employment (n = 7) – was inconsistent and often descriptive, limiting cross-study comparisons. A minority of studies reported mental health or genetic-specific variables – such as affected gene (n = 6) antidepressant use (n = 3) or proximity to onset (n = 3).

Narrative Synthesis

A narrative synthesis approach was employed to integrate qualitative and quantitative findings. This approach allowed for the identification of four core themes that captured key aspects of the psychological experience of at-risk individuals: psychological responses to genetic risk, systemic and relational factors which shape psychological experience, coping strategies and support needs, and intervention approaches for individuals at risk.

Psychological Responses to Genetic Risk

13 studies – 10 qualitative and three mixed-methods – contained interview or survey data highlighting experiences of anxiety, distress, or fear related to the future when living at risk

(Axelman et al., 2003; Boutte, 1990; Cooper et al., 2024; Dratch et al., 2024; Etchegary, 2011; Garcia-Toro et al., 2020; Gluyas et al., 2023; Ho et al., 2011; Howard et al., 2024; Quaid et al., 2008; Velissaris et al., 2023; Wauters & Hoyweghen, 2021; Wieringa et al., 2022). Participants in several of these studies described heightened distress from hyper-attunement to potential signs of disease onset such as forgetfulness or balance issues. However, one study also suggested that some individuals found symptom-monitoring reassuring (Dratch et al., 2024).

In contrast, studies assessing psychological outcomes were mixed. Several studies using standardised measures found that most at-risk individuals scored within normal ranges on outcomes such as depression, wellbeing, and life satisfaction (A'Campo et al., 2012; Cecchin et al., 2007; Bergman et al., 2017; Poos et al., 2023; Velissaris et al., 2023). However, one large study found that 9.1% of at-risk individuals reported suicidal ideation – slightly higher than general population estimates (Paulsen et al., 2005; Samples et al., 2025). Only a few studies examined whether demographic factors influence psychological outcomes in those at risk, with mixed results. Bergman et al (2017) suggested both gender (being male) and proximity to onset (being past the average age of onset) predicted greater psychological health satisfaction. Other studies reported no significant effects of age, sex, or education (Cecchin et al., 2007; van der Meer et al., 2014).

Four studies included comparisons between at-risk individuals and non-clinical control groups, which varied from general population samples to partners (see Table 1) (Axelman et al., 2003; Chisholm et al., 2013; Swearer et al., 2001; van der Meer et al., 2014). Only one found poorer outcomes in the at-risk group, including greater attachment anxiety and reduced mental health (van der Meer et al., 2014). The others reported broadly comparable outcomes, or in two cases, more favourable results. For example, Chisholm et al. (2023) found greater positive affect in untested at-risk individuals compared to controls, and Axelman et al. (2003)

reported better quality of life in relationships and everyday life compared with a population sample, despite nearly 90% expressing anxiety about future disease onset.

The variability in psychological outcomes may reflect the fluctuating salience of genetic risk which was widely reported across studies. Seven interview studies highlighted triggers such as approaching the expected age of onset, witnessing a relative become symptomatic, or making decisions about relationships and parenthood (Boutte, 1990; Cooper et al., 2024; Dratch et al., 2024; Etchegary, 2009, 2011; Howard et al., 2024; Quaid et al., 2008). Similarly, Swearer et al. (2001) reported that nearly half of participants had experienced emotional distress at some point, often related to a family member's illness, despite not finding poorer outcomes overall. Nine studies contained participant interview data highlighting how risk status can influence major life decisions, including relationships, careers, and reproductive choices (Boutte, 1990; Cooper et al., 2024; Dratch et al., 2024; Etchegary, 2011; Gluyas et al., 2023; Howard et al., 2024; Quaid et al., 2008; Wauters & Hoyweghen, 2021 Wieringa et al., 2022).

Systemic and Relational Factors which Shape the Psychological Experience

Systemic and relational factors were demonstrated as central to the psychological experience of living at risk. 10 studies – eight qualitative and two quantitative – highlighted the added distress of having a symptomatic relative (Boutte, 1990; Cooper et al., 2024; Dratch et al., 2024; Etchegary, 2011; Garcia-Toro et al., 2020; Quaid et al., 2008; Swearer et al., 2001; van der Meer et al., 2014; Wauters & Hoyweghen, 2021; Wieringa et al., 2022). For example, van der Meer et al. (2014) found that those at risk who had grown up with an affected parent reported more adverse childhood experiences and parental dysfunction than their partners.

Six qualitative studies further described psychological challenges such as caregiving burden, confronting a potential future self, disease reminders, and grief (Cooper et al., 2024;

Dratch et al., 2024; Etchegary, 2011; Garcia-Toro et al., 2020; Quaid et al., 2008; Wieringa et al., 2022). However, four interview studies also reported perceived benefits of growing up in an affected family such as stronger family bonds, increased disease knowledge, enhanced caregiving skills, and hope, particularly if other family members experienced late onset (Boutte, 1990; Etchegary, 2009; Garcia-Toro et al., 2020; Wieringa et al., 2022).

Secrecy surrounding genetic risk was also prominent across many of the studies. Eight interview studies reported decisions to withhold information about genetic risk due to stigma, fear of relationship strain or abandonment, or to protect others (Boutte, 1990; Cooper et al., 2024; Etchegary, 2009, 2011; Garcia-Toro et al., 2020; Gluyas et al., 2023; Quaid et al., 2008; Velissaris et al., 2023; Wauters & Hoyweghen, 2021). Conversely, one study also described how some individuals instead opt for deliberate openness as a challenge to familial secrecy (Wauters & Hoyweghen, 2021).

Interview data reflected significant distress about the impact of genetic risk on others, especially fears of transmission, witnessing decline, or becoming a burden (Boutte, 1990; Dratch et al., 2024; Etchegary, 2011; Garcia-Toro et al., 2020; Gluyas et al., 2023; Ho et al., 2011; Howard et al., 2024; Quaid et al., 2008; Wauters & Hoyweghen, 2021). This was also present in quantitative findings. Bilal et al. (2024), for example, identified "passing on the gene" and "impact on relationships" as frequent stressors among those at risk, with this future-oriented stress significantly associated with depression. Similarly, Axelman et al. (2003) reported that three-quarters of participants were highly anxious about their children's risk.

Psychological Coping Strategies and Support Needs

Nine qualitative studies reported that at-risk individuals try to focus on living fully and maintaining hope, particularly regarding future medical advancements or delayed onset (Boutte, 1990; Cooper et al., 2024; Dratch et al., 2024; Etchegary, 2009, 2011; Gluyas et al.,

2023; Howard et al., 2024; Quaid et al., 2008; Wieringa et al., 2022). Avoidance was also commonly described as a coping mechanism in eight qualitative studies, with three suggesting that distancing from risk-related concerns helped preserve normalcy (Cooper et al., 2024; Etchegary, 2009; Quaid et al., 2008).

The importance of social support emerged as a key theme. Eight studies, including qualitative and mixed-methods intervention research, highlighted how peer networks offered valued connection and shared understanding (Cooper et al., 2024; Eccles et al., 2021; Etchegary, 2009; Garcia-Toro et al., 2020; Gluyas et al., 2023; Poos et al., 2022; Velissaris et al., 2023; Wauters & Hoyweghen, 2021). However, four studies also noted that some individuals found peer interaction distressing, as it reinforces disease awareness (Boutte, 1990; Eccles et al., 2021; Etchegary, 2009; Gluyas et al., 2023).

Practical coping strategies such as maintaining health, financial planning, information seeking, and research participation were described by participants in seven interview studies (Axelman et al., 2003; Cooper et al., 2024; Dratch et al., 2024; Etchegary, 2009; Gluyas et al., 2023; Howard et al., 2024; Wauters & Hoyweghen, 2021). A smaller number of interview studies referenced maladaptive coping, such as substance use or engaging in reckless behaviours (Boutte, 1990; Howard et al., 2024; Quaid et al., 2008).

Although many studies emphasised the importance of professional support, participants frequently described unmet support needs or dissatisfaction (Axelman et al., 2003; Cooper et al., 2024; Dratch et al., 2024; Etchegary, 2009; Garcia-Toro et al., 2020; Howard et al., 2024). Two studies described specific requests from participants, including better information on early signs and treatment options, support with financial and legal planning, and strategies for managing distress (Axelman et al., 2003; Gluyas et al., 2023).

Intervention Approaches for Individuals at Risk

Five studies investigated interventions to support individuals at risk; all were exploratory, single-group designs. Most were small scale, though two included larger samples of approximately 100 participants (A'Campo, 2012; Gluyas et al., 2023).

Mindfulness was the most frequently studied intervention, with three studies (one qualitative, two mixed-methods) reporting benefits such as reductions in perceived distress, improved emotion regulation, and greater present-moment awareness (Eccles et al., 2021; Poos et al., 2022; Velissaris et al., 2023). However, adherence to home practice was a common challenge (Eccles et al., 2021; Velissaris et al., 2023). The two studies which measured quantitative outcomes demonstrated an improvement in some mindfulness skills, however, mood outcomes were mixed – Poos et al (2022) found significant improvements in depression and anxiety two months post intervention, while Velissaris et al (2023) reported no differences which they suggested could be due to floor effects because of low scores at baseline.

Information-based or psychoeducational interventions were also positively received by those at risk, particularly for providing up-to-date information and stress-management guidance. A'Campo (2012) found significant post-intervention improvements in coping for participants after engaging in a patient education programme, particularly in seeking social support, but no change in psychological outcomes. Attendance rates for these interventions varied across the included studies – Gluyas et al. (2023) reported strong attendance, while A'Campo (2012) found a 39% dropout rate among those at risk.

Across interventions, participants valued peer connection and preferred being grouped with others at similar stages, and not symptomatic. However, some participants reported anxiety in advance of attending (Eccles et al., 2021; Gluyas et al., 2023). Online delivery was identified as a promising approach for broader accessibility (Eccles et al., 2021; Gluyas et al., 2023; Poos et al., 2022).

Discussion

This scoping review identified 24 studies published between 1990 and 2024 that explored the psychological experiences of individuals living at risk for an ADNC. Notably, almost half were published in the past five years, reflecting growing interest in this field. Most studies (50%) used qualitative designs to explore the lived experience of being at risk, while a third (33%) were cross-sectional quantitative studies assessing psychological outcomes such as depression, anxiety, and quality of life. A smaller number (17%) employed mixed methods, and five studies evaluated the feasibility or acceptability of psychological interventions, all of which were exploratory in nature.

Summary of Findings

The findings suggest that the psychological experience of living at risk for ADNCs is multifaceted and shaped by a combination of individual and systemic factors. These include early life experiences, individual differences, access to social and psychological support, and broader family dynamics. Those at risk often witness the progression of the same disease in affected relatives and may assume caregiving responsibilities, compounding psychological distress.

The included studies demonstrate that responses to genetic risk are highly individualised. While some people engage in avoidance or suppression to preserve a sense of normalcy, others adopt proactive strategies such as lifestyle changes, future planning, and seeking support. Many individuals move between these approaches at different times. Qualitative findings indicate that the consequences of living with genetic risk may become particularly salient during major life transitions – such as reproductive decision-making, the illness of a relative, or entering a new relationship. These findings align with broader literature on rare disorders, suggesting that both the rarity and the hereditary nature of ADNCs may contribute to a distinct and complex psychological burden (von der Lippe et al., 2017).

However, inconsistencies across the literature limit the ability to draw definitive conclusions about the psychological impact of living at risk. While some studies reported no significant psychological differences between at-risk individuals and control groups, others identified substantial levels of distress. This variability may reflect several factors. Cross-sectional designs may fail to capture the dynamic and context-dependent nature of psychological responses, and standardised measures may lack sensitivity to the complex, ambiguous, and often hidden burdens of being at risk (Poos et al., 2022).

Gaps in Existing Research

The review highlights several gaps in the literature. Firstly, no longitudinal studies were identified to offer an understanding of how psychological outcomes might change over time or at different life stages. Without such studies, it is difficult to interpret qualitative findings about the fluctuating salience of genetic risk or to identify when support may be most needed

Secondly, sample sizes across the literature were relatively small: almost three quarters of studies included fewer than 50 at-risk participants, and most intervention studies (four of five) included fewer than 20. While this likely reflects the rarity of many ADNCs, it restricts generalisability and may have reduced statistical power to detect meaningful effects, particularly in the single-group intervention studies where the absence of comparison groups further limits interpretation. Notably, those who choose to participate in research may be those with better coping abilities, introducing potential selection bias and limiting the representativeness of current findings.

Thirdly, most existing studies treat at-risk participants as a homogeneous group, with inconsistent reporting of clinical and demographic factors such as ethnicity, education, socioeconomic status, and relationship status. However, research on chronic health conditions suggests these variables can significantly influence coping, access to support, health literacy, and experiences of stigma (Helgeson & Zajdel, 2017; Audulv, 2014). Only a small number of

studies quantitatively assessed how factors such as age, gender, education, or proximity to estimated age of onset shape psychological outcomes for those at risk, and findings were inconsistent. A recent review of neurological conditions highlights the need to move beyond individual or family-level perspectives to consider the impact of broader societal factors such as social marginalisation linked to poverty or ethnic minority status (Audulv, 2014). Among the studies that did report ethnicity, most reported that the majority of participants were White, reflecting the broader overrepresentation of WEIRD (Western, Educated, Industrialized, Rich, and Democratic) populations in genetic research (Oliveri et al., 2018; Wainstein et al., 2022). This lack of diversity restricts the cross-cultural applicability of findings and obscures how social and structural factors may shape the psychological experience of genetic risk.

A final gap in the current literature is its disproportionate focus on HD. Almost two-thirds of the studies in this review focused on HD, yet no studies were identified that explore the psychological experience of living at risk for rarer ADNCs such as inherited prion diseases or Familial Parkinson's Disease. This imbalance, also noted in previous reviews, underscores the need for broader research across ADNCs (Crook et al., 2022; Paulsen et al., 2013). While ADNCs share common features that allow for comparisons between conditions, each also presents distinct challenges related to symptomatology, age of onset and public perceptions (McAllister et al., 2007). For example, the stigma associated with inherited prion disease due to the Bovine Spongiform Encephalopathy (BSE) epidemic, which was widely sensationalized in the media, may shape distinct psychological experiences (Bechtel & Geschwind, 2013).

Directions for Future Research

Despite ongoing uncertainty about the precise psychological impact of living at risk, the findings demonstrate that at-risk individuals face unique challenges and often lack adequate

psychological support. Some included studies identified potentially helpful forms of support; however, only five directly evaluated interventions, and all were preliminary in nature. These mostly used either qualitative methods or small-scale, single-group quantitative designs, limiting conclusions about causality or effectiveness.

Future research should prioritise the development and rigorous evaluation of evidence-based interventions tailored to the needs of individuals living at risk for ADNCs. Such studies should incorporate appropriate comparison groups and longitudinal follow-up, which are currently lacking. Flexible trial designs – including adaptive, crossover, and early escape methods – have been recommended in rare disease contexts where research is challenged by small sample sizes and clinical heterogeneity and may offer feasible and efficient alternatives to traditional RCTs (Whicher et al., 2018).

Finally, many studies reported that at-risk individuals struggle to access professionals who understand the complexities of genetic risk. This need for better-informed professional support echoes findings from the broader rare disease literature. A systematic review by von der Lippe et al. (2017) highlighted that knowledge about rare diseases is often limited, not only among the public but also among healthcare professionals. Enhancing professional education around ADNCs and their psychological implications may help close this gap and ensure that individuals receive timely, appropriate, and sensitive support.

Limitations of this review

Several limitations of this review should be acknowledged. First, the search may not have been exhaustive, as non-English language sources were excluded, along with studies that did not explicitly focus on psychological experiences as a primary aim or research question. This may have led to the omission of relevant studies where psychological aspects were discussed but not clearly framed.

Second, distinguishing preclinical symptoms from psychological responses to living at risk remains challenging as some ADNCs involve early psychological changes that may overlap with disease onset. Despite exclusion criteria designed to address this, differentiating psychological adjustment from early disease indicators remains a key limitation in this field.

Third, scoping review methodology does not typically involve a formal quality assessment of included studies, in line with JBI guidelines (Pollock et al., 2023). While this enhances inclusivity, it may limit the interpretability and generalisability of findings, particularly in terms of study quality. As research in this field advances, a systematic review methodology may be more appropriate for assessing the quality of evidence.

Finally, this review did not specifically search for intervention studies. As such, some relevant work in this area may not have been captured. A focused synthesis of intervention strategies would be valuable as the evidence base expands to better understand what support might be helpful for these individuals.

Conclusion

To the author's knowledge, this is the first review to systematically map the available literature in this area, identifying key patterns, gaps, and directions for future research. It provides important insights into the complex and dynamic experience of living at risk for an ADNC, highlighting the emotional uncertainty, impact on self-identity, and evolving support needs individuals may face across the life course. The review contributes to a broader understanding of how those living at risk navigate genetic uncertainty, family dynamics, and life planning – whether or not they have undergone genetic testing. Importantly, it includes the perspectives of untested individuals, who have historically been underrepresented in the literature, and expands the focus beyond testing decisions to consider the full spectrum of lived experience (Baldwin et al., 2024; Crook et al., 2017; Crozier et al., 2015; Greaves & Rohrer, 2019: Mahmood et al., 2022; Zarotti et al., 2020)

The review highlights critical gaps in the literature, including no longitudinal studies, small sample sizes, reliance on qualitative methodologies, lack of control groups, and the overrepresentation of HD, which together limit the generalisability and applicability of current findings. More research is urgently needed to better understand the psychological impact of living at risk, compare experiences across different conditions, and develop effective, tailored interventions. By synthesising the current evidence, this review lays a foundation for more inclusive, targeted, and methodologically robust research that can ultimately improve psychological support for individuals facing the challenges of autosomal dominant inherited neurodegenerative risk.

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Part 2: Empirical Paper

Acceptability and Feasibility of a Brief, Multi-Component Acceptance and Commitment Therapy (ACT) Intervention to Support Those Living At Risk of Inherited Prion Diseases

Abstract

Aims: Prion diseases are rare, fatal neurodegenerative conditions caused by misfolded prion proteins. While those with sporadic forms experience little warning, individuals at risk for inherited prion diseases (IPD) – which account for approximately 10–15% of all cases – live with prolonged uncertainty that can lead to psychological distress. Despite this, there is limited understanding of what psychological support may be beneficial. Acceptance and Commitment Therapy (ACT), a values-based intervention that promotes psychological flexibility, has shown promise in managing distress in health conditions characterised by uncertainty. This study evaluated the feasibility and acceptability of a brief, multi-component ACT-based intervention for individuals at risk of IPD. **Method:** A non-randomised, parallel-group feasibility and acceptability trial was conducted using a waitlist control design. Adults living at risk of IPD in the UK (either gene-positive and asymptomatic or untested) were assigned to the intervention or control group based on availability. The intervention comprised a 30-minute psychoeducation video, a five-hour in-person workshop, and a one-hour remote booster session . Quantitative data were collected at baseline, one month, and three months post-intervention. Qualitative feedback was obtained from intervention participants two months post-intervention. Predefined progression criteria guided feasibility evaluation including recruitment and retention rates, time to complete measures, and proportion of missing data. Acceptability was assessed using an adapted Theoretical Framework of Acceptability questionnaire. **Results:** All five progression criteria were met. 29 participants were recruited (15 intervention, 14 control), with a 58% recruitment rate, 80% intervention completion, 10% missing data, and retention exceeding the predefined 70% threshold. All participants rated the intervention as acceptable, though variability emerged across TFA dimensions such as burden, ethicality and self-efficacy. Qualitative feedback indicated the workshop was relevant, practical, and timely, though preferences varied

regarding timing and content focus. Exploratory analyses suggested improvements in psychological quality of life over time in the intervention group. **Conclusions:** A single-session ACT workshop is feasible and acceptable for individuals at risk of IPD. Findings support progression to a randomised controlled trial and underscore the need for flexible, tailored psychological support in rare genetic conditions.

Introduction

Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are rare, fatal neurodegenerative disorders caused by the accumulation of misfolded prion proteins in the central nervous system. Recognised in both animals and humans, they can arise in three distinct ways: sporadically, with no identifiable cause; acquired**,** through exposure to infectious prions via medical procedures or contaminated animal products; or inherited**,** due to pathogenic mutations.

Inherited Prion Diseases

Inherited prion diseases (IPD) account for approximately 10-15% of all prion disease cases (Mead et al., 2019). IPDs are autosomal dominant conditions caused by over 60 known mutations in the gene that encodes the prion protein, the PRNP (Mead et al., 2019). This results in a wide spectrum of clinical phenotypes, with considerable variability in age of onset, symptom presentation, and rates of progression – even among individuals in the same family carrying the same mutation (Goldman & Vallabh, 2022). Despite this variability, common symptoms include progressive cognitive decline, changes in mood and behaviour, difficulties with coordination and movement, and muscle jerks or seizures (Mead et al., 2019).

IPD primarily presents in three forms: genetic Creutzfeldt-Jakob disease (gCJD), fatal familial insomnia (FFI), and Gerstmann-Sträussler-Scheinker (GSS) syndrome (Zerr & Schmitz, 2003). While some phenotypes closely resemble sporadic forms of prion disease in their rapid progression, others follow a more protracted course, mimicking disorders such as Alzheimer's disease or frontotemporal dementia (Goldman & Vallabh, 2022). For most mutations, penetrance is believed to be complete, meaning that individuals who carry the mutation are expected to develop symptoms at some point in their lives (Zerr & Schmitz, 2003).

As there are currently no effective treatments that alter the course of prion diseases, care primarily focuses on managing symptoms and maintaining quality of life (Trevitt & Collinge, 2006). Living with an incurable, degenerative condition has profound psychosocial consequences for both patients and their families, who frequently take on caregiving responsibilities (Ford et al., 2019; Klockgether et al., 2019; Roos, 2010; Silva et al., 2020). In IPD, this burden is likely intensified by their genetic nature and extreme rarity**,** with an estimated 303 families affected in the UK, representing approximately 1,091 individuals and a lifetime risk of about 1 in 60,000 (Corbie et al., 2022). Research into both genetic and rare diseases highlights common concerns about stigma and discrimination, including fears of being misunderstood by the public and healthcare professionals (Atkins & Padgett, 2024; von der Lippe et al., 2017; Wauters & Hoyweghen, 2021).

Prion diseases may carry additional layers of stigma due to their historical association with the Bovine Spongiform Encephalopathy (BSE) epidemic – widely sensationalized in the media as "mad cow disease" – as well as ongoing restrictions on blood, organ, and tissue donation for those living in IPD families due to a theoretical risk of transmission (Bechtel & Geschwind, 2013). Research demonstrates that individuals affected by both inherited and acquired forms experience fear of judgment or differential treatment, which can discourage them from disclosing their risk status, even to healthcare professionals (Elam et al., 2011; Schwartz et al., 2019).

The Psychological Experience of Living At Risk of Inherited Prion Diseases

The psychological challenges associated with IPD often begin long before the onset of clinical symptoms (Owen et al., 2014; Schwartz et al., 2019). Due to its autosomal dominant inheritance pattern, first-degree relatives of affected individuals have a 50% chance of carrying the pathogenetic mutation. These individuals – often referred to as "at risk" or, if tested, "confirmed mutation carriers" – live with the ongoing uncertainty of whether and

when they will develop a rare, incurable condition they likely have already witnessed in close relatives (Schwartz et al., 2019). In this study, the term “at risk” will refer to both untested individuals with a confirmed family history of IPD and those tested positive for the mutation but currently asymptomatic.

Advances in predictive genetic testing now allow at-risk individuals to determine whether they carry a pathogenic variant; however, uptake in IPD remains relatively low, with only around 25% choosing to be tested (Owen et al., 2014). Decision-making surrounding genetic testing is complex and shaped by a combination of personal and familial factors including concerns about the psychological impact of knowing, the absence of effective treatments, fears of stigma and discrimination, and the belief that it may be easier to live with uncertainty than the certainty of a positive result (Crook et al., 2021; Mendes et al., 2019; Owen et al., 2014; Schwartz et al., 2019).

Even among those who undergo testing and are found to be positive for a gene mutation, uncertainty remains a defining feature of life for those at risk of IPD (Schwartz et al., 2019). They do not know when or if symptoms will appear, or which symptoms may develop. This uncertainty is compounded by wide variability in age of onset, with standard deviations of up to 11 years from the mean (Goldman & Vallabh, 2022). As a result, evidence suggests there are psychological consequences, regardless of whether one chooses to undergo testing (Owen et al., 2014; Schwartz et al., 2019).

A recent small study found that levels of anxiety were elevated across all groups examined within IPD families – those who declined testing, confirmed mutation carriers, and noncarriers – compared to the general population (Schwartz et al., 2019). Symptoms of depression also appear to be more common among IPD at-risk individuals (Owen et al., 2014). In addition, qualitative findings highlight a range of psychological challenges, including persistent fear of disease onset, obsessive self-monitoring, uncertainty around

family planning, experiences of stigma and secrecy, and difficulties disclosing genetic risk to children or extended family (Schwartz et al., 2019).

While these findings provide useful insights, the existing literature on prion disease has predominantly focused on medical aspects, with limited attention to the psychosocial implications of living at risk. Research in other inherited neurodegenerative conditions – such as Huntington's disease (HD), familial frontotemporal dementia (FTD), and familial Alzheimer's disease – has revealed similar psychosocial challenges, including fluctuating distress shaped by individual circumstances and life events (Bergman et al., 2017; Boutte, 1990; Cooper et al., 2024; Dratch et al., 2024; Etchegary, 2009, 2011; Howard et al., 2024; Quaid et al., 2008; Swearer et al., 2001). For instance, Dratch et al. (2024) found that individuals at risk for FTD and amyotrophic lateral sclerosis experienced these conditions as identity threats, with perceived risk and emotional impact shifting over time due to ongoing uncertainty and fear of symptom onset. Nonetheless, even within these better-studied conditions, psychosocial research remains relatively sparse, leaving much unknown about the full impact of genetic risk and how best to support this distinct patient population.

Interventions to Support Those At Risk of Genetic Neurological Conditions

To the author's knowledge, there is no published research investigating psychological support for individuals at risk of IPD or prion diseases more broadly. In related genetic neurodegenerative conditions, specific support needs have been identified as being potentially helpful, such as help with preparing for legal and financial challenges, managing emotional distress, and coping with uncertainty about disease onset (Gluyas et al., 2023). Some preliminary studies have also begun to explore supportive approaches in other at-risk populations including mindfulness-based interventions, psychoeducational forums, and relationship-focused approaches (Eccles et al., 2021; Gluyas et al., 2023; Petzke et al., 2022; Poos et al., 2022; Velissaris et al., 2023). Mindfulness-based interventions, in particular,

have demonstrated several potential benefits including reduced distress, anxiety, and depression, improved emotion regulation, and increased peer support (Eccles et al., 2021; Poos et al., 2022; Velissaris et al., 2023). However, the evidence base remains limited by small sample sizes, a lack of control groups, and heterogeneity in intervention formats.

Even in HD, a more prevalent genetic neurodegenerative disease, findings are mixed and support for at-risk individuals remains scarce (Zarotti et al., 2020). This likely reflects a combination of challenges also relevant for IPD including the rarity of these conditions, stigma and taboo, high attrition in longer-term interventions, and avoidance of psychological distress.

Approaches such as cognitive behavioural therapy (CBT), acceptance and commitment therapy (ACT), and psychoeducation have demonstrated efficacy in symptomatic populations affected by HD, motor neuron disease (MND), multiple sclerosis (MS), Parkinson's disease (PD), and dementia (Pinto et al., 2023; Zarotti et al., 2020, 2021a, 2021b, 2023). However, there is a clear need to investigate evidence-based psychological interventions for at-risk populations. A recent review highlighted the promise of transdiagnostic, third-wave therapies such as ACT in addressing the emotional challenges of living with long-term neurological conditions (Robinson et al., 2019). These approaches may well be suited to individuals at risk of such conditions.

Acceptance and Commitment Therapy for Those At Risk of Inherited Prion Diseases

Given the limited support available for individuals at risk of IPD, those seeking psychological care outside the genetic testing process largely access standard NHS talking therapies. These typically follow traditional CBT models focused on challenging unhelpful thoughts, behavioural modification, or symptom reduction (Beck, 2011). However, because concerns of at-risk individuals often stem from rational fears and ongoing uncertainty, traditional CBT may be less suitable (Dratch, L. et al., 2024; Etchegary, 2009; Schwartz et

al., 2019). The rarity and complexity of IPD further highlights the need for more specialist, tailored approaches.

ACT, often considered a third wave cognitive behavioural approach, has gained recognition as an alternative to CBT, particularly for individuals facing chronic, uncontrollable stressors (Cullen, 2008; Gould et al., 2024). Rather than aiming to reduce or eliminate distress, ACT promotes psychological flexibility, encouraging individuals to engage in meaningful, values-based actions in the presence of difficult thoughts and emotions (Hayes et al., 2011). This makes it particularly relevant for conditions like IPD, which involve persistent uncertainty (Graham et al., 2016; Gould et al., 2024). Its transdiagnostic framework is also well-suited to address the diverse psychological needs of this population.

Systematic reviews and meta-analyses have demonstrated ACT's effectiveness across a wide range of chronic conditions – including cancer, diabetes, HIV, chronic pain, and epilepsy – improving outcomes such as depression, anxiety, distress, sleep, and quality of life (Graham et al., 2016; Hughes et al., 2017; Konstantinou et al., 2023; Li et al., 2021; Ye et al., 2024). Its application in neurological and neurodegenerative diseases is also growing, with encouraging findings in conditions such as motor neuron disease, multiple sclerosis, Parkinson's disease, and HD (Gould et al., 2024; Schriger et al, 2025; Sheppard et al., 2010; Zarotti et al., 2021a).

To date, the evidence-base for ACT in neurological populations focuses on multi-session, one-on-one format delivery. However, a less intensive approach may be better suited for those at risk of IPD, where resources are limited and geographically dispersed, making multiple sessions less feasible. Flexibility is essential for psychological interventions in healthcare, especially for long-term and neurodegenerative conditions (Carroll et al., 2021; Pinto et al., 2023). Similarly, studies targeting individuals at risk of other neurodegenerative

diseases have highlighted the importance of flexible support that minimally disrupts work and family life (Eccles et al., 2021; Gluyas et al., 2023).

In single-session format, ACT has shown promise in reducing psychological distress and may be more feasible and acceptable than multi-session models for this population (Dochat et al., 2021). One-day ACT workshops have been used effectively across a range of medical and psychiatric conditions – including diabetes, multiple sclerosis, migraine, inflammatory bowel disease, and cardiovascular disease – due to their adaptability, cost-effectiveness, and time efficiency (Dindo et al., 2015; Gregg et al., 2007; Lillis et al., 2009; Sheppard et al., 2010). Framing such interventions as "workshops" rather than "therapy" may also reduce stigma, better align with expectations in primary care, and improve uptake (Dindo et al., 2017). Research involving at-risk populations has similarly highlighted the benefits of group formats in reducing isolation and stigma, and in fostering motivation and shared understanding (Eccles et al., 2021; Gluyas et al, 2023; Poos et al., 2022; Velissaris et al., 2023).

Rationale for Current Study

The present study aims to investigate the feasibility and acceptability of a brief, multi-component ACT-based intervention for those living at risk of IPD. The programme comprised three elements: (1) a 30-minute psychoeducation video sent one week prior to the workshop to introduce key concepts; (2) a five-hour, in-person ACT-based group workshop; and (3) a one-hour remote booster session delivered four weeks later to reinforce learning and support continued practice. The brief, accessible format was designed to improve treatment reach, enhance completion rates, and reduce burden, particularly for individuals in rural areas or those experiencing functional barriers to care (Arcury et al., 2005).

In addition to assessing feasibility and acceptability, the study will assess whether a brief ACT-based intervention improves psychological outcomes using self-reported outcome measures. Given the lack of existing research in this area, the findings could have broader

implications for developing scalable, accessible psychological support for individuals at risk of other rare genetic neurological conditions.

Method

Methods and reporting were guided by the Consolidated Standards of Reporting Trials (CONSORT) 2010 extension for pilot and feasibility trials and the Template for Intervention Description and Replication (TIDieR) guidelines, both recommended for non-randomised feasibility studies (Eldridge et al., 2016; Hoffmann et al., 2014; Lancaster & Thabane, 2019).

Formal hypothesis testing for effectiveness was not conducted, in line with recommendations for pilot and feasibility trials, which are not typically powered for efficacy assessment (Eldridge et al., 2016).

Study Design

This was a non-randomised, parallel-group feasibility and acceptability trial with a waitlist control design. An intended allocation ratio of 1:1 was used. Participants were allocated to either the intervention group (receiving the ACT workshop) or a waitlist control group (treatment as usual), based on availability to attend. The study aimed for group sizes between five to 10 participants.

The study originally intended to use randomisation, but this was amended after recruitment began due to logistical constraints. First, the project needed to be delivered within a fixed timeframe agreed with stakeholders, meaning workshop dates had to be scheduled in advance. Participants' availability varied considerably, and some were unable to attend any of the earlier sessions. To ensure their inclusion within the project window, these individuals were allocated to the waitlist control group rather than being randomised. Second, a proportion of participants were members of the same families. Several requested to be allocated together for mutual support, while others asked to be separated to allow for independent participation. Accommodating these preferences was important both ethically

and practically, given the sensitive nature of the topic and the small, highly specialised participant pool. Taken together, these factors meant that true randomisation was unfeasible. Instead, participants were allocated pragmatically in order to maximise recruitment, minimise attrition, and ensure that the project could be delivered successfully within the constraints of the agreed timeframe.

Eligibility criteria were revised during the trial. Initially, only individuals scoring above clinical cut-off on the Depression Anxiety Stress Scales-21 (DASS-21) at screening were eligible. The DASS-21 is a 21-item self-report scale measuring current depression, anxiety, and stress as indicators of psychological distress (Henry & Crawford, 2005). However, due to high interest from those below the threshold – and recognising that the salience of genetic risk and psychological impact fluctuate over time – criteria were expanded to include all interested individuals regardless of mood symptom severity (Dratch et al., 2024; Etchegary, 2011; Howard et al., 2024; Quaid et al., 2008). This decision was also informed by ethical considerations about withholding access.

This study was funded by the CJD Support Network to support the delivery of the ACT workshops, including participant expenses.

Participants

Recruitment was conducted through the National Prion Clinic (NPC) and its National Prion Monitoring Cohort (NPMC), a UK-wide longitudinal observational study established in 2008. The NPMC systematically collects prospective data on individuals diagnosed with or at risk of developing prion disease, including asymptomatic carriers of pathogenic PRNP mutations. Ethical approval for the NPMC was obtained from the Scotland A Research Ethics Committee (Ref: 05/MRE/0063). The present nested study was approved as an amendment to the original protocol by the Health Research Authority and Health and Care Research Wales on September 4, 2024 (Appendix D). Additional recruitment was conducted via

advertisements on the CJD Support Network social media channels – a UK charity that supports all forms of CJD and prion disease – and interested individuals not already part of the NPMC were invited to enrol before participation.

Participants were asymptomatic adults in the UK living at risk of IPD, either tested and positive for the gene mutation or untested, who could provide informed consent and attend the workshop in person. Exclusion criteria included active IPD symptoms, current suicidal ideation, severe mental health conditions requiring more intensive support, or significant cognitive impairment that could affect meaningful participation. Eligibility was screened when participants were first contacted about the study, and asymptomatic at-risk status was confirmed at recruitment by the NPC clinical team and monitored throughout the study.

Recruitment and Allocation Procedure

All eligible participants were contacted by phone, or email if unreachable by phone. Information sheets were emailed to those who expressed interest (Appendix E).

Interested individuals were asked to complete an online availability survey and provide informed consent via an online consent form (Appendix F). Participants were assigned to a group based on availability, and allocation remained fixed thereafter. Two intervention group participants who did not attend their assigned workshop were excluded from per-protocol analyses.

Measures were completed online via Qualtrics at three time points: T1 (two weeks pre-workshop), T2 (four weeks post-workshop), and T3 (three months post-workshop). One reminder email was sent to non-responders.

Intervention

The intervention was a brief, multi-component ACT-based programme delivered in three parts. First, participants were sent a 30-minute psychoeducational video one week before the workshop to provide an overview of current research on IPD and the practical aspects of

living at risk. Based on service user feedback, this was provided in advance to establish a common foundation of knowledge without detracting from the core therapeutic content.

Second, participants attended a five-hour, face-to-face ACT group workshop at the NPC in London. Content was adapted from established single-session ACT protocols for other populations and refined with input from service users and clinicians (as described below), to address the specific needs of this population (Dindo et al., 2019, 2023). Three workshops were delivered between November 2024 and January 2025 by a Clinical Psychologist and a Trainee Clinical Psychologist, ranging from three to five participants per group. These followed a structured agenda covering all six core processes of ACT – acceptance, cognitive defusion, contact with the present moment, self as context, values, and committed action – and incorporating didactic teaching, experiential exercises, and group reflection to enhance psychological flexibility (Hayes et al., 2011). Core components included values clarification, identification of avoidant coping, and acceptance and mindfulness practices. A detailed description of the content and exercises is provided in Appendix G, and participants received a workshop manual to take home (Appendix H).

Finally, a one-hour booster session was delivered four weeks post-workshop, either online or by phone, based on participant preference. The booster was designed to reinforce skills learned, identify barriers to implementation, and encourage ongoing practice. A standardised list of discussion topics guided delivery (Appendix I).

Following completion of the intervention arm, control group participants were given the opportunity to receive the full intervention.

Intervention Development and Training

Two focus groups including individuals at risk of IPD, recruited from the NPC, were conducted during the study preparation phase to refine workshop content and participant materials. The first group (n = 5) engaged in a structured discussion on gaps in knowledge

related to living at risk and some of the practical and emotional challenges. This was used to inform what should be included in the psychoeducation component of the intervention. The second group (n = 2) provided feedback on the draft workshop agenda and manual. Participants from the first focus group were invited to take part in the study, as they were not exposed to any intervention materials, while those in the second group were not invited, due to their familiarity with the finalised content. One of the six participants from the first focus group later participated in the trial as a member of the Control group. Their inclusion was based on ethical considerations around fair access, as excluding eligible individuals solely due to their early involvement in shaping the intervention was considered inequitable. As they did not receive the intervention, the risk of contamination was judged to be minimal.

Facilitators achieved ACT Level 1 accreditation and completed a two-day training course on delivering ACT in single-session workshop form. A pilot session was delivered to NPC staff, with anonymous feedback informing final workshop adjustments.

Intervention adherence protocol

All workshops were audio recorded and securely stored. Adherence to ACT protocols was assessed by an independent reviewer, not directly involved in the research, using a pre-developed checklist to assess whether facilitators covered the six core processes of ACT as part of each workshop (see Appendix J).

Outcomes and measures

Primary outcomes related to feasibility and acceptability. A mixed-methods approach was used to integrate quantitative and qualitative data (Aschbrenner et al., 2022).

Feasibility outcomes included:

- Recruitment metrics (number eligible/ineligible; reasons for ineligibility or declining participation)
- Completion rates for workshop and booster session

- Attrition and retention rates at each time point
- Time taken to complete main outcome measures
- Proportion of missing data

Acceptability outcomes included:

- Participant ratings across seven components of acceptability – affective attitude, burden, ethicality, intervention coherence, opportunity cost, perceived effectiveness, and self-efficacy – measured using an adapted version of the Theoretical Framework of Acceptability (TFA) questionnaire post-workshop (Sekhon et al., 2022; see Appendix K).
- Qualitative feedback collected three months post-intervention via structured telephone interviews or written open-ended responses, based on participant preference. All intervention group participants were invited to take part via email, with reminders sent to maximise uptake. Of the 13 participants invited, six provided feedback. The limited uptake may have introduced bias in the qualitative findings. The interview guide is available in Appendix L.

  Informal assessment of ACT skill use, captured during the booster session. Participants reflected on their use of strategies, and responses were documented and retrospectively coded by the facilitator on a 4-point scale indicating degree of ACT skill application (see Appendix M for scale).

A priori feasibility and acceptability criteria were established to guide progression decisions and establish whether the study could be delivered successfully. This included: (a) ≥50% of contacted individuals consent to participate, (b) ≥70% retention at follow-up, (c) ≥70% of intervention participants will have a median score of ≥4 on the TFA, (d) ≤10% missing data and (e) ≥80% intervention completion rate. These criteria align with guidance for pilot and feasibility studies, including CONSORT recommendations, which emphasise the

importance of defining thresholds for recruitment, retention, intervention adherence, and acceptability before the study begins (Eldridge et al., 2016; Mellor et al., 2023; Pearson et al., 2020). In the absence of directly comparable studies, thresholds were determined by incorporating stakeholder input, as recommended for feasibility studies, to consider what was practically achievable and meaningful for assessing feasibility and acceptability in this context (Mellor et al., 2023; Pearson et al., 2020).

Outcome Measures

Standardised self-report measures were selected to assess psychological distress, psychological flexibility, and quality of life, consistent with prior ACT intervention research (Dochat et al., 2021):

- Depression Anxiety Stress Scales-21 (DASS-21): A 21-item self-report scale measuring current depression, anxiety, and stress as indicators of psychological distress. It has strong internal consistency, high reliability, and established validity, and is widely used in clinical trials, including single-session ACT studies (Dochat et al., 2021; Henry & Crawford, 2005; Lee et al., 2019).
- Comprehensive Assessment of Acceptance and Commitment Therapy Processes (CompACT): A 23-item self-report measure of psychological flexibility across openness to experience, behavioural awareness, and valued action, rated on a 7-point Likert scale. It demonstrates strong internal consistency, good test–retest reliability, and convergent validity with other ACT measures (Bayliss, 2018; Francis et al., 2016).
- World Health Organization Quality of Life-BREF (WHOQOL-BREF): A 26-item self-report measure assessing quality of life across physical, psychological, social, and environmental domains. It has demonstrated good internal consistency, test–retest

reliability, and content and discriminant validity (Skevington et al., 2004; WHOQOL Group, 1998).

Intervention participants additionally completed:

- ACT Session Questionnaire (ACT-SQ)**:** A post-session comprehension check measuring delivery of ACT's six core processes (Probst et al., 2020).
- A researcher-developed feedback questionnaire which aimed to capture information on previous psychological support and engagement with the psychoeducational video (Appendix K).

Sample Size

In line with current guidance for feasibility studies, no formal sample size calculation was conducted. The study instead followed the commonly recommended target of a minimum of 12 participants per group (Julious, 2005).

Analytical Methods

Feasibility and TFA data were analysed descriptively and narratively. Qualitative data were analysed using inductive thematic analysis, a flexible, data-driven approach (Braun & Clarke, 2006). Interviews were transcribed verbatim, and initial codes were generated independently by the first author. Codes were then discussed with the supervisor to resolve any disagreements, and themes were iteratively refined. These discussions helped maintain reflexivity and reduce bias.

Group differences on baseline variables were assessed using independent samples t-tests for continuous variables and chi-square tests for categorical variables. Normality and homogeneity of variance assumptions were checked using Shapiro-Wilk and Brown-Forsythe tests, respectively. When assumptions of normality or equal variances were violated, alternative analyses such as Welch's t-test or Mann-Whitney U tests were conducted as appropriate.

Mixed-measures ANOVAs were conducted to evaluate Time (T1, T2, T3), Condition (Intervention, Control), and interaction effects on DASS-21, CompACT, and WHOQOL-BREF scores.

Given the small sample size and the exploratory nature of this pilot study, analyses were intended to be hypothesis-generating rather than confirmatory. As such, corrections for multiple comparisons, such as Bonferroni adjustment, were not performed, as these would have been overly conservative and risked overlooking potentially meaningful patterns. Consequently, findings should be interpreted with caution.

Results

Participant Characteristics

Participant demographics are summarised in Table 1. 29 participants (10 men, 19 women) aged 19 to 70 years (M = 44.3, SD = 13.7) were allocated to a study condition. A range of gene mutations was represented across groups, including E200K, P102L, D178N, and several rarer variants. The average proximity to age of onset – calculated as the difference between participant age and the mean age of onset for their gene mutation – was 13.2 years (range = -8.7-42.3, SD = 14.4) (Goldman & Vallabh, 2022). Among those tested, the time since testing ranged from <1 to 24 years (M = 7.24 years) at the start of the intervention. Most participants identified as White British; one participant identifying as having an Other Mixed ethnic background.

Groups were generally well matched; however, the intervention group included significantly more tested individuals (87%, 13 out of 15) than the control group (50%; 7 of 14): $\chi^2(1, N = 29) = 4.55$, $p = .033$. No other demographic or clinical characteristics differed significantly between groups (all ps > .09).

According to the post workshop questionnaire, six of the 13 (46%) participants who took part in the intervention had previously received psychological support, but none had experience with ACT.

Table 1

Participant Characteristics

Condition	Gene mutation	Gender	Age	Testing status	Proximity to average age of onset (y)
Intervention	E200K	Male	23	Untested	38.3
Intervention	E200K	Male	67	Tested+	-5.7
Intervention	E200K	Female	30	Tested+	31.3
Intervention	E200K	Female	51	Tested+	10.3
Intervention	E200K	Female	50	Tested+	11.3
Intervention	E200K	Male	43	Tested+	18.3
Intervention	E200K	Female	40	Tested+	21.3
Intervention	P102L	Female	60	Tested+	-6.3
Intervention	P102L	Male	39	Untested	14.7
Intervention	P102L	Female	53	Tested+	0.7
Intervention*	P102L	Female	54	Tested+	-0.3
Intervention	P102L	Male	28	Tested+	25.7
Intervention	D178N	Female	48	Tested+	3.3
Intervention	6-OPRI	Female	32	Tested+	3.1
Intervention*	Q212P	Female	55	Tested+	Unknown
Control	E200K	Male	38	Tested+	23.3
Control	E200K	Female	20	Untested	41.3
Control	E200K	Female	50	Tested+	11.3
Control	E200K	Male	41	Tested+	20.3
Control	E200K	Female	70	Tested+	-8.7
Control	E200K	Female	48	Untested	13.3
Control	E200K	Male	19	Untested	42.3
Control	P102L	Male	34	Untested	19.7
Control	P102L	Female	59	Untested	-5.3
Control	P102L	Female	35	Untested	18.7
Control	D178N	Female	48	Tested+	3.3
Control	D178N	Male	49	Tested+	2.3
Control	5-OPRI	Female	37	Untested	9.8
Control	E146G	Female	50	Tested+	Unknown

Note. Proximity calculated as the difference between participant age and the mean age of onset for their gene mutation in years (Goldman & Vallabh, 2022)
*Participants who did not attend the workshop and are excluded from analyses.

Feasibility

All a priori feasibility targets were evaluated and successfully met. Recruitment exceeded the target, with 58% of eligible participants enrolling (target ≥50%). Intervention completion reached 80% (target ≥80%), and retention at T3 was 79% (target ≥70%). The proportion of missing data was 10%, meeting the target of ≤10%. Details for each target are presented in Table 2.

Participant flow is summarised in Figure 1. Of the 61 individuals contacted, 59 were eligible and 34 consented, yielding a recruitment rate of 58%. Reasons for ineligibility included recent symptom onset and cognitive comorbidities. Among those eligible but not recruited 13 declined participation – citing timing conflicts, no perceived need for the intervention, or concerns about burden – and 12 were uncontactable.

Five participants withdrew after consenting but before allocation, resulting in 29 participants (85%) assigned to study arms (15 intervention, 14 waitlist control). Two participants initially assigned to the intervention group withdrew prior to the workshop – one due to availability, the other due to concerns about participation – and were reassigned to the waitlist group for scheduling purposes but excluded from primary outcome analyses. Of the remaining 13 intervention participants, all completed the workshop, and 12 (92%) completed the booster call, resulting in an overall full intervention completion rate of 80% based on the 15 originally assigned.

Retention rates exceeded the *a priori* target of ≥70% at follow-up, with measure completion rates of 93% at T1, 97% at T2, and 79% at T3. The higher rate at T2 reflects some participants who missed T1 but returned at follow-up. Retention was calculated at each time point based on the original sample (N = 29) to allow for such variations.

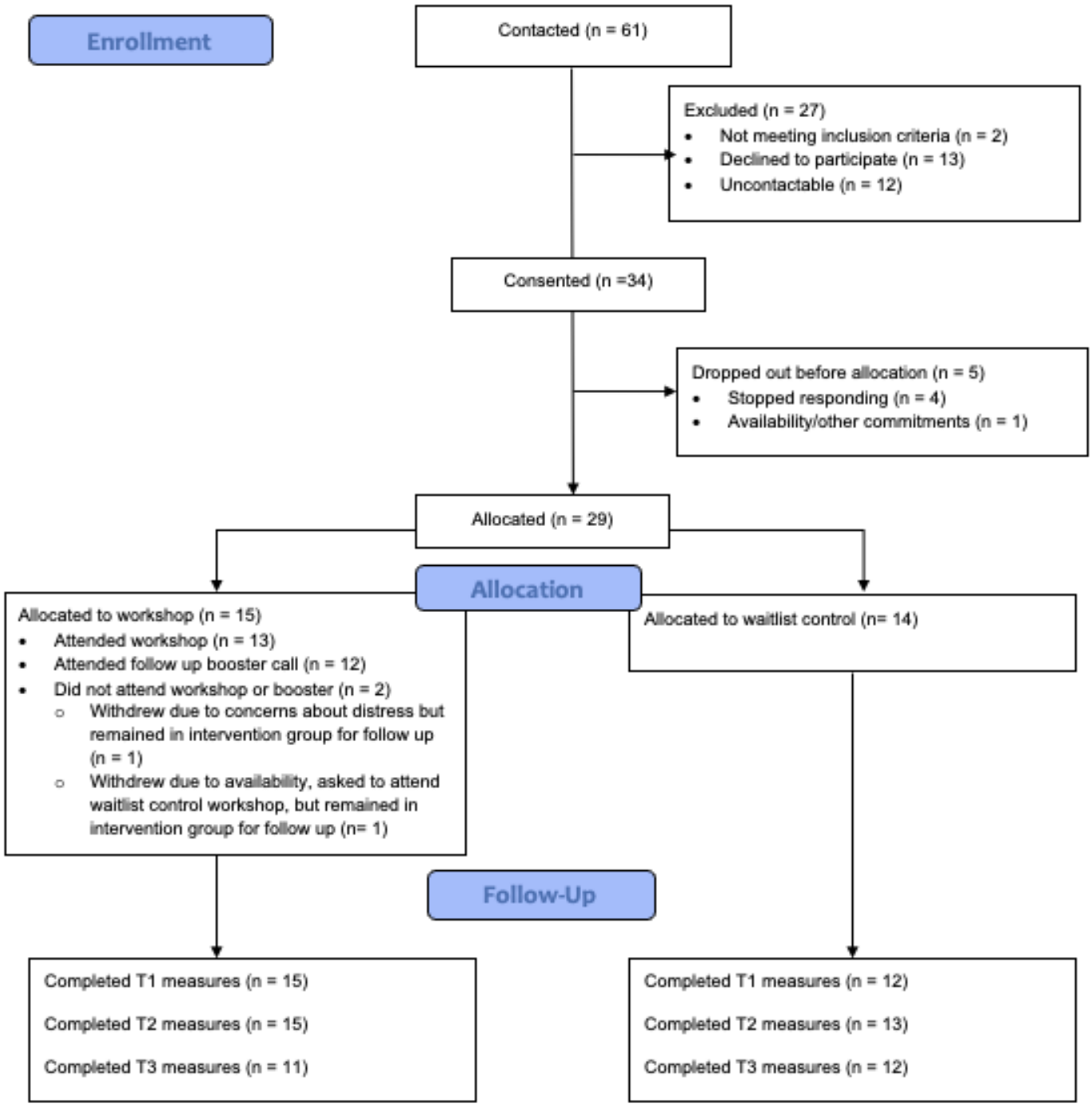
Table 2

Feasibility Targets and Observed Outcomes

Feasibility Target	Target	Observed	Met?
Recruitment rate	≥50%	58%	Yes
Intervention completion	≥80%	80%	Yes
Retention at T3	≥70%	79%	Yes
Missing data	≤10%	10%	Yes

Figure 1

CONSORT flow diagram of participant recruitment, allocation and follow-up



Mean completion times for the outcome measures indicated low participant burden and supported their feasibility: 2.7 minutes for the DASS-21 (SD = 1.4, range = 0.9–7.5), 5.5 minutes for the CompACT (SD = 4.3, range = 1.1–36.2), and 3.6 minutes for the WHOQOL-BREF (SD = 2.1, range = 1.2–12.0).

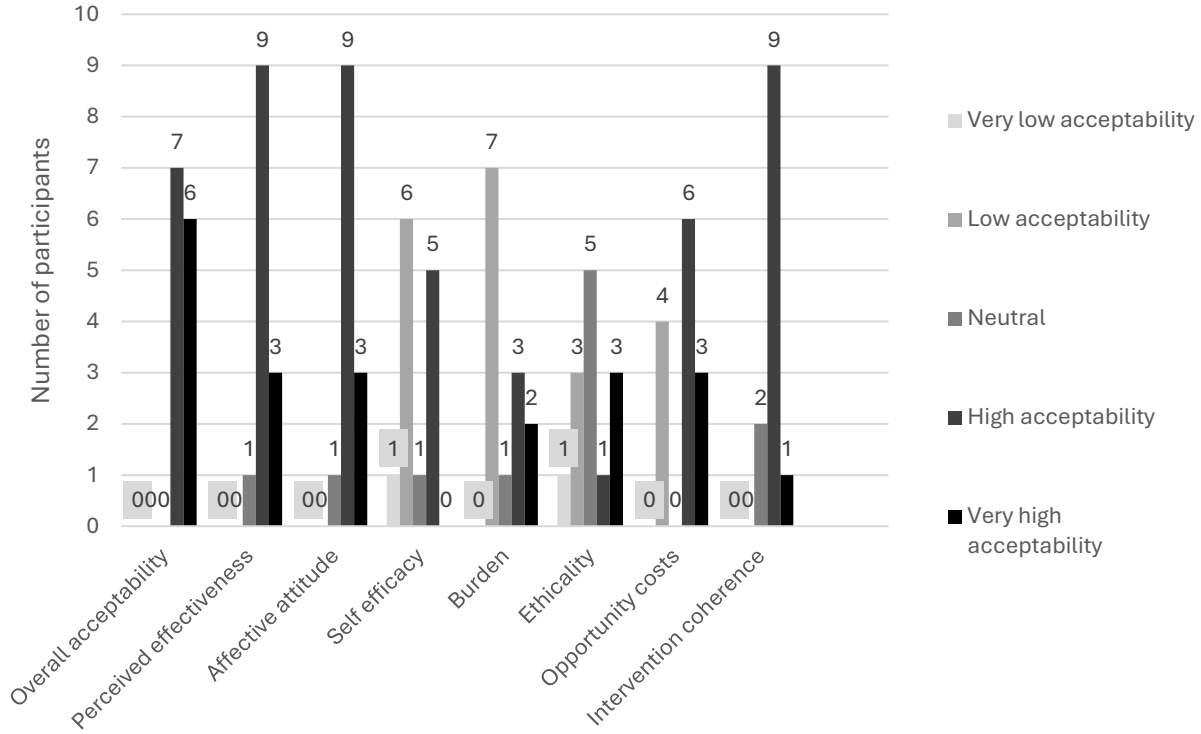
Across all time points (T1–T3), nine out of 87 expected questionnaire sets (29 participants × three time points) were not completed, resulting in an overall missing data rate of 10%. As the questionnaires were delivered via an online platform requiring item completion to proceed, missingness reflected full non-completion at a time point rather than partial data. Specifically, two participants did not complete the measures at T1, one of whom was also missing at T2. At T3, six other participants did not complete the measures.

Acceptability

The *a priori* acceptability criterion – ≥70% of intervention participants will have a median score of ≥4 on the TFA (high or very high) – was met. Specifically, 11 out of 13 participants (85%) had a median score of 4 or above when scores were aggregated across all eight constructs. All 13 participants rated the intervention as acceptable or completely acceptable, with a mean overall acceptability score of 4.46. Ratings were particularly high for perceived effectiveness, affective attitude, and intervention coherence, where most participants gave high or very high scores. In contrast, domains such as burden, self-efficacy, ethicality, and opportunity cost showed more varied responses, with several participants reporting higher perceived effort, lower confidence, or ethical concerns. Full response distributions are presented in Figure 2.

Figure 2

Theoretical Framework of Acceptability: Ratings by Domain (n = 13)



Note. Domains such as burden and opportunity cost were reverse scored so that higher ratings reflect greater acceptability. One participant did not provide a rating for intervention coherence.

Participant Engagement and Adherence

Five participants reported watching the psychoeducational video, though only three watched it in full. Among those who did not watch the video: five cited lack of time, one did not think it would be useful, and two provided no reason.

The six core processes of ACT were covered in each of the three workshops as assessed by an independent reviewer using a checklist (see Appendix J). Participants indicated mostly good engagement with ACT processes during the workshop: Median scores across the six core ACT-SQ dimensions ranged from 2 ("applies fairly well") to 3 ("applies to a great extent") (see Table 2). The highest mean score (2.85) was observed for the item *"to recognise what is important to me in my life and what gives orientation to my life,"* suggesting strong resonance with the values component of ACT. Other items showed moderate to high mean and median scores, reflecting varying but overall positive participant responses.

Assessment of ACT skill application was conducted for all Intervention participants who attended the one-month booster session (n = 12). Retrospective coding of participant reflections by facilitators (see Appendix M) demonstrated that all participants used ACT skills following the workshop: 17% reported frequent use of ACT principles, 58% moderate use, and 25% minimal or inconsistent use. The most reported strategies included values-based decision-making, committed action and defusion techniques.

Thematic Analysis of Participant Feedback

All participants from the intervention group (n = 13) were invited to provided qualitative feedback post workshop. Six participants provided feedback through structured telephone interviews (n = 3) or open-ended response forms (n = 3). Four themes relevant to intervention acceptability were developed through thematic analysis and are summarised in Table 3 with

associated subthemes and illustrative quotes. As feedback was collected anonymously, pseudonyms are used.

Table 3

Acceptance and Commitment Therapy Session Questionnaire Ratings (ACT-SQ)

ACT-SQ Item	Median	Mean	Range
To accept unpleasant feelings, thoughts, or body sensations rather than fight them	2	1.92	0–4
To gain inner distance from unpleasant feelings, thoughts, or body sensations and observe them	3	2.15	0–3
To stay in the here and now (present moment)	3	2.62	1–3
To realise that feelings, thoughts, and body sensations are part of me, but I am more than these	2	1.77	0–4
To recognise what is important to me and what gives orientation to my life	3	2.85	1–4
To act in daily life according to what is important and what gives orientation	3	2.62	0–4

Note. Scores based on participants who completed the intervention (N = 13). Scores range from 0 ("does not apply at all") to 4 ("applies extremely"). Range represents range of scores seen.

Table 4

Themes and Illustrative Quotes from Participant Interviews

Themes	Subthemes	Example quotes
1. Structure and delivery	1.1 Session length and timing	"It was a long day… around the four-hour mark would be ideal." (Martin) "It was about right" (Thomas)
	1.2 Group size and interaction	"Felt safe to chat and express how we felt" (Alice) "A balance between intimate space and more people." (Caroline)
	1.3 Facilitation experience	"Relaxed and funny and made it interesting at a level to suit us all" (Alice) "There were times I felt [the facilitator] wasn't listening to us and had in [their] head what [they] wanted to say." (Caroline)
2. Workshop experience	2.1 Social connection	"A good opportunity to meet others" (Martin) "The girl sitting next to me said, well her life has changed so she may want to rethink that… and I hadn't even thought about that" (Caroline)
	2.2 Expectations versus reality	"I was expecting to have more chat around the condition" (Alice) "And it's like, ooh this is awkward are we not supposed to talk about it?" (Caroline)

		2.3 Engagement with ACT	"Gives you the opportunity to look at what your barriers are and maybe change them" (Caroline) "Identify the difference between carrying something…but not being consumed by it." (Craig)
3	Usefulness and relevance	3.1 Perceived value and resonance	"Useful as it can provide ways to deal with difficult feelings and emotions that can come up around it." (Ellie) "Some parts were very helpful, some parts I never really understood" (Thomas)
		3.2 Practical tools and takeaways	"It has given me some strategies" (Alice) "Good for everyday life" (Ellie)
		3.3 Follow up call and materials	"Good to catch up…and work though some of my thoughts after." (Alice) "I haven't used it since attending…but it is a good thing to have." (Ellie)
4	Improvements for the future	4.1 Depends on stage of journey	"More useful for people who are recently coming to the diagnosis." (Thomas) "I'd quite like to do it again further down the line." (Caroline)
		4.2 Suggested refinements	"I think if they did make reference to the reason why we were there…that would be powerful" (Caroline) "More check in sessions / booster calls over a longer period of time" (Craig)

Note. Names are pseudonyms assigned for anonymity. These are not linked to participant IDs used elsewhere in the study.

Theme One: Structure and Delivery. Most participants found the length of the workshop and the follow-up call appropriate. Caroline reflected, “It was for the right amount of time,” while Martin appreciated the workshop being delivered in one session: “Positive that it was one block...better than if it had been shorter sessions spread out.” However, two participants suggested minor adjustments. One remarked, “It was a long day… around the four-hour mark would be ideal,” while another felt that an additional hour would have allowed more material to be covered.

All participants appreciated the small group format, which was described as supportive and conducive to sharing: “It was a nice small group so didn’t feel overwhelming,” and “the small group meant that people were quite open.” However, one participant emphasised that diversity was also important given the genetic nature of the condition: “Small groups are good but a balance between intimate space and more people.”

Views on facilitation were generally positive, with participants highlighting a relaxed and engaging delivery style: “Both facilitators were very good, relaxed and funny and made it interesting at a level to suit us all.” Another participant reflected that the facilitators “covered a difficult subject with the right blend of humour and sensitivity.” However, one participant expressed concern about facilitation being overly directed at times, stating, “There were times I felt [the facilitator] wasn’t listening to us and had in [their] head what [they] wanted to say.”

Theme Two: Workshop Experience. Participants highlighted the value of social connection and shared experience during the workshop. Martin noted, “Hearing other people’s perspectives, looking at how they are feeling,” while another participant reflected it was helpful to hear from others to gain a new perspective on dealing with some of the challenges related to living at risk: “And I hadn’t even thought about that.”

Expectations about workshop content varied. Half of the participants noted they anticipated more focus on prion disease: “I was expecting to have more chat around the condition… to speak with those other members about how we felt and lived with the condition.” Others expressed feeling unsure what to expect, but said they were ultimately satisfied with the content: “I was not 100% sure what to expect, but it met with what I hoped it would cover.”

Engagement with ACT components was high. Participants reflected on key learnings such as “letting thoughts come and go” and “focusing on the more important things.” Thomas remarked that “writing down a goal and how to get there was useful,” while another participant noted it was helpful to, “Identify the difference between carrying something… but not being consumed by it.”

Theme Three: Usefulness and Relevance. Most participants reflected on finding the workshop useful. Craig described it as “very useful professionally and personally,” while Alice noted it “gave me some strategies to use.” Although some elements resonated more than others – “some parts were very helpful, some parts I never really understood” – overall, the material was considered applicable: “The strategies are good for everyday life”.

The follow-up call and printed materials were also well-received. All participants said they found the follow-up call helpful, and five of six described the manual as useful either for the present or future. Ellie described the booster session as “good to catch up and work through some of my thoughts,” while others valued the handbook as an ongoing resource: “Very clear, descriptive, and informative but easy to follow. I’ve used it since and would revisit it if I had struggles.”

Theme Four: Improvements for the Future. Participants reflected on the timing and potential future use of the workshop. One person commented, “I think it would be more

useful for people who are recently coming to the diagnosis," while another said, "I'd quite like to do it again further down the line." There were also suggestions for improvement, such as integrating more discussion around experiences of living at risk: "If they did make [more] reference to the reason why we were there… that would be powerful." Others recommended structural refinements, including more regular check-ins and face-to-face delivery for follow-ups.

Preliminary findings

Baseline comparisons revealed no statistically significant group differences across outcome measures (all $p > .05$). However, physical quality of life ($p = .082$), psychological quality of life ($p = .062$), and social quality of life ($p = .073$) approached significance, with moderate to large effect sizes (Cohen's d ranging from –0.73 to –0.79). In all these cases, the Control group had higher mean scores at baseline (see Table 4 for descriptive statistics). These findings suggest potential group differences worth further exploration in larger samples. Minor violations of normality were observed for DASS subscale scores, and unequal variance for social quality of life; these were addressed via nonparametric and Welch-adjusted analyses, respectively, yielding consistent results.

Primary analyses using mixed-measures ANOVAs assessed changes in psychological distress (DASS-21), psychological flexibility (CompACT), and quality of life (WHOQOL-BREF) across three Time points (T1, T2, T3) and between Conditions (intervention and waitlist control). A significant Time by Condition interaction was observed for psychological quality of life, $F(2, 34) = 5.59$, $p = .008$. This interaction reflects a consistent improvement in psychological quality of life in the Intervention group from T1 to T3 (M = 55.13 to 62.50), while scores in the Control group remained relatively stable over time. Assumption checks indicated no violation of sphericity (Mauchly's $p = .291$), and Levene's tests supported equality of variances across groups.

All other main and interaction effects were non-significant (all $p > .10$). However, mean scores generally showed improvement from T1 to T3 in the Intervention group, while scores in the Control group either declined or remained stable. This pattern was observed across several outcomes including: total distress on the DASS-21; total psychological flexibility and the three subscales of the CompACT (valued action, openness to experience, and behavioural awareness); and all four domains of the WHOQOL-BREF (psychological, environmental, social, and physical quality of life). Depression and anxiety scores improved slightly in both groups by T3, whereas stress scores worsened slightly for both.

For the Intervention group specifically, most scores peaked at T3, suggesting continued improvement over time and after the follow-up booster session, rather than immediate post-workshop gains. An exception was social quality of life, which was higher for Intervention participants at T2 than T3. Notably, openness to experience and CompACT total scores initially decreased slightly at T2 but demonstrated an improvement by T3 compared with T1.

Preliminary findings must be interpreted with caution, as the study was not powered to detect effectiveness and multiple outcomes were measured.

Table 5

Descriptive Statistics for Outcomes by Condition and Timepoint (N = 27)

Measure	Condition	T1 M (SD)	T2 M (SD)	T3 M (SD)
DASS-Total	Control	23.50 (23.94)	21.39 (16.09)	24.50 (18.05)
	Intervention	25.69 (22.57)	24.62 (28.30)	24.67 (15.88)
Depression	Control	8.00 (9.54)	6.92 (7.01)	7.83 (7.93)
	Intervention	9.69 (9.72)	8.92 (11.30)	8.22 (5.87)
Anxiety	Control	6.00 (7.68)	4.00 (5.23)	5.33 (5.14)
	Intervention	5.39 (5.86)	4.92 (9.76)	4.67 (4.80)
Stress	Control	9.50 (8.87)	10.46 (5.72)	11.33 (7.40)
	Intervention	10.62 (8.06)	10.77 (8.31)	11.78 (6.59)
CompACT-Total	Control	94.17 (20.05)	95.00 (14.85)	90.67 (15.63)
	Intervention	84.93 (20.68)	83.85 (25.21)	90.56 (23.03)
Valued Action	Control	36.92 (6.36)	36.54 (3.87)	36.25 (6.47)
	Intervention	33.54 (5.16)	35.00 (6.46)	35.22 (8.06)
Openness to Experience	Control	37.42 (11.04)	38.39 (9.30)	36.50 (8.54)
	Intervention	34.92 (12.78)	32.46 (13.50)	36.11(10.90)
Behavioural Awareness	Control	19.83 (7.57)	20.08 (5.68)	17.92 (6.54)
	Intervention	16.46 (7.17)	16.39 (7.25)	19.22 (6.70)
WHOQOL-BREF domains				
Physical QoL	Control	78.27 (12.32)	76.92 (13.80)	75.30 (14.24)
	Intervention	68.41 (14.57)	68.68 (19.47)	71.82 (17.54)
Psychological QoL	Control	68.06 (14.58)	65.71 (15.04)	66.67 (13.41)
	Intervention	55.13 (18.01)	59.62 (17.71)	62.50 (16.80)
Social QoL	Control	77.78 (11.42)	78.21 (11.56)	75.70 (17.57)
	Intervention	62.82 (25.60)	68.59 (21.83)	64.81 (25.61)
Environmental QoL	Control	76.31 (13.36)	76.20 (10.56)	75.26 (18.91)
	Intervention	66.59 (15.38)	65.39 (17.19)	70.14 (16.76)

Note. Values represent mean scores and standard deviations (in parentheses) by condition and timepoint.

Discussion

This study demonstrates the feasibility and acceptability of a brief ACT intervention for individuals at risk of IPD, with all five predefined targets met. Recruitment and retention were strong, and all participants rated the intervention as acceptable. However, variability in some TFA constructs, including ethicality, burden, opportunity cost, and self-efficacy suggests these areas warrant further exploration in future trials. A more nuanced, multidimensional assessment of acceptability – across timepoints and using mixed methods – may offer deeper insight into different constructs and how perceptions evolve.

The findings suggest participants found the workshop engaging and relevant, with ACT strategies resonating with the challenges of living at genetic risk. However, some wanted the content to be more focused on prion disease, aligning with the wider literature on neurodegenerative conditions, which highlights the importance of tailoring psychological interventions to the condition and context (Pinto et al., 2023). Despite this, only 38% of intervention participants reported watching the pre-workshop psychoeducation video, which may have addressed this need. The reasons for low engagement with this element of the intervention – such as time constraints, avoidance, ambivalence, or format preferences – should be further investigated before a full trial.

Peer interaction was described as particularly beneficial, echoing findings from interventions targeted at other at-risk populations such as HD (Eccles et al., 2021; Gluyas et al., 2023; Poos et al., 2022; Velissaris et al., 2023). However, informal feedback indicated that some participants preferred to be grouped with others of similar testing status or gene variant, reflecting the heterogeneity within this population (Goldman & Vallabh, 2022). Future research should explore the specific contributions of group dynamics versus ACT content in driving therapeutic benefit. Encouragingly, ACT process measures indicated engagement with core psychological flexibility processes both during the workshop and in

the four weeks afterwards. However, some ACT principles appeared to resonate more strongly with participants than others, particularly values-based actions. It would be useful to investigate whether this reflects differences in workshop content or facilitation style, or whether values-based actions inherently hold greater relevance for individuals at risk. Such insights could inform tailoring of intervention components to maximise engagement and effectiveness.

Preliminary Clinical Signals

Although this study was not powered to detect efficacy, exploratory analyses suggested improvements in psychological quality of life over time in the intervention group. While group-level effects on other outcomes were not significant, these preliminary patterns nonetheless highlight meaningful individual differences in response which underscore the need for tailored support and should be investigated further as part of a full trial.

Qualitative feedback reinforced these signals and participants suggested that the workshop may be most beneficial at transitional moments – such as nearing estimated age of symptom onset - when the emotional salience of genetic risk may be heightened (Dratch et al., 2024; Etchegary, 2011; Howard et al., 2024). At the same time, some participants shared more informally during the workshop discussion that they would have found the intervention helpful earlier on. This variability may support a flexible, self-directed approach, allowing individuals to engage when the content feels most personally relevant. Importantly, timing strategies should remain inclusive of untested individuals, who may experience significant distress despite not undergoing formal testing (Schwartz et al., 2019). Larger-scale studies will be needed to determine whether outcomes differ based on timing of intervention – such as proximity to symptom onset or recent testing – which could not be explored in depth in this pilot study due to the small sample.

Implications for Future Research and Trial Design

This study offers several key insights to inform the development of a future full-scale trial:

- **Eligibility and Targeting:** Although many participants did not meet clinical thresholds for anxiety or depression, they still reported finding the intervention beneficial. This suggests that strict symptom cut-offs may not be necessary for inclusion. Given the fluctuating nature of distress in this population, a more flexible approach to eligibility may be warranted (Dratch et al., 2024; Etchegary, 2011; Howard et al., 2024; Quaid et al., 2008).
- **Timing of Delivery:** Participants differed in when they felt the intervention would be most useful. Some suggested it would be most helpful during transitional moments (e.g., post-testing, approaching symptom onset), while others wished it had been available earlier. This heterogeneity suggests that offering the intervention at multiple points and allowing self-selection may enhance relevance and accessibility.
- **Involvement of Family Members:** Several participants informally expressed interest in including partners or other relatives. This aligns with research showing that family members and tested non-carriers can also experience significant distress in the context of inherited neurodegenerative conditions (Schwartz et al., 2019; Sobel & Cowan, 2000).
- **Measurement of Distress:** Minimal change in quantitative outcomes may reflect challenges in capturing the psychological experiences of those living at risk. Standardised mood questionnaires, which typically capture symptoms over short timeframes, may not adequately reflect the unique and often ambiguous experiences of individuals living at risk (Poos et al., 2022). This highlights the need for complementary qualitative methods and the development of more sensitive or

condition-relevant measures – for example, disease-specific stressor checklists as used in HD populations (Bilal et al., 2023).

- **Group Composition and Format:** While peer interaction was widely valued, some participants preferred groups stratified by testing status or gene variant. Future delivery models could explore more tailored groupings to optimise comfort and relevance.
- **Condition-Specific Content:** Some participants felt the workshop lacked prion-specific content. Since few watched the pre-session video, integrating psychoeducation into the workshop itself may improve engagement and better meet this need.
- **Trial Design and Randomisation:** While randomisation was not feasible in the current study, it will be essential in a future efficacy trial. This may require alternative recruitment strategies, more flexible delivery options, or blinded waitlist allocation to maintain feasibility and acceptability.

Limitations

As a feasibility study, the small sample size and absence of power calculations limit the reliability and generalisability of observed effects. The lack of randomisation is another limitation. Group allocation was pragmatic to accommodate scheduling and maximise recruitment, but this may have introduced selection bias. While baseline comparisons revealed no statistically significant group differences across outcome measures, physical, psychological, and social quality of life scores approached significance, with moderate to large effect sizes favouring the control group. This pattern suggests that group differences may have been present but undetectable due to limited statistical power. Future studies should prioritise randomisation to reduce baseline imbalances and strengthen internal validity.

The use of multiple outcome measures raises the possibility of inflated type I error. Floor and ceiling effects may also have occurred, as many participants scored within the 'normal' range and only a small number scored in the 'severe' range on several measures.

The sample was primarily drawn from a highly engaged research cohort, which may limit generalisability to less engaged or harder-to-reach individuals who could have different needs or levels of distress. This may have also influenced the recruitment rate for the study, which should be carefully considered before progressing to a full trial, especially given the rarity of IPD. The sample also included a higher proportion of tested individuals (69%) than would be expected based on broader population estimates, which may further skew findings (Owen et al., 2014). Evidence suggests that those who undergo testing tend to cope better psychologically, potentially inflating perceived acceptability or benefit (Goldman, 2020; Tibben, 2007).

Finally, only six of the 13 participants invited to complete qualitative interviews participated. This limited uptake may have introduced bias in the qualitative findings, as those who agreed to be interviewed could differ systematically from non-participants, potentially affecting the representativeness of the themes identified.

Conclusion

To the author's knowledge this is the first psychological intervention study for individuals at risk of IPD. Despite methodological limitations, findings support the feasibility and acceptability of a brief ACT-based intervention and provide preliminary indications of benefit for some participants. The single-session format offers a practical, resource-efficient model for delivering psychological support in rare conditions such as IPD where specialist access is limited.

Mixed feedback in areas such as timing, group composition, and content emphasis highlights the heterogeneity of this population and the need for flexible, tailored approaches

in future research. These findings lay the groundwork for a randomised controlled trial and offer early guidance for the development of supportive interventions in other rare genetic conditions where psychological care remains underdeveloped (Zarotti et al., 2020). If effective, this intervention could also promote intergenerational resilience by equipping individuals with coping strategies that have the potential to extend beyond the individual.

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Part 3: Critical Appraisal

Overview

This critical appraisal reflects on and evaluates the process of conducting and writing up the empirical study included in part two. Drawing on my experiences as both a clinician and a researcher, I explore key practical and emotional challenges and summarise learnings which will inform my approach to research and clinical work moving forward.

The reflections included are drawn from my research journal, notes from supervisory meetings, and dedicated time at the end of the project to step back and evaluate the work holistically – something which was often difficult to do throughout. This reflection generated four core themes: 1) Rigorous project planning and design; 2) Methodological compromises; 3) Evolving as a researcher; and 4) Reflections on the emotion challenges of facilitation.

Rigorous Project Planning and Design

Research success can be largely determined in the planning stages and a well-thought-out plan is therefore essential to ensure a project is both manageable and methodologically sound (O'Leary, 2007). On taking time at the end of this project to reflect, I am reminded of the importance of the very beginning stages which laid the foundations for what I was able to achieve.

I began the project as a novice in both research and the clinical area of prion disease. Research demonstrates that many psychologists can find developing a research project demanding or daunting, something which reflects my own experiences (Cooper & Graham, 2009). Although I had some experience with neurodegenerative conditions, working with individuals at genetic risk for prion disease was entirely new. This lack of familiarity was particularly challenging in the early stages, where foundational decisions had long-term implications for the research.

One of the initial challenges I faced was a delay in the ethics approval process, which prevented me from progressing with the research as quickly as I had hoped. At the time, I felt

significant pressure to begin; being part of a cohort of 80 other students conducting projects of similar scale inevitably invited comparisons. In retrospect, however, these delays proved unexpectedly beneficial. They gave me the opportunity to take a more thoughtful and measured approach, carefully planning contingencies in case the project encountered unforeseen issues or became unfeasible. Although these contingencies were ultimately not required, having them in place provided a sense of reassurance and helped me maintain momentum throughout the project.

During the ethics review period, I used the time to apply for funding from the CJD Support Network (CJDSN), a charity supporting the population involved in this research. Securing this funding significantly expanded the scope of what we were able to deliver. The importance of both research funding and collaboration with patient organisations in the context of rare diseases is well documented (Griggs et al., 2009; Smith & Thew, 2017). In this study, the funding enabled us to offer the intervention in person by covering participants' travel and accommodation expenses. While there had initially been discussion about delivering the workshop online, my subsequent experience of facilitating the five-hour in-person session made it clear that an online format might have reduced the intervention's acceptability and limited opportunities for peer connection, something participants identified as highly valuable. In addition, the support and insights provided by CJDSN were instrumental in deepening my understanding of the research population and refining the intervention during the pilot phase, based on their feedback.

Building Relationships with the Clinical Team

During the planning phase of the project, I also spent time fully embedding myself within the National Prion Clinic (NPC) team and this proved vital in later stages – particularly during recruitment, as it was clinicians who had the trusted relationships with potential participants. Guidance suggests that a researcher has a responsibility to form good working

relationships when conducting research in clinical teams, which includes efforts to understand the client group and their team as well as to demonstrate why the research is needed in the first place (Williams et al., 2020).

As part of embedding myself into the team at the NPC, I proactively sought opportunities to observe clinical practice and meet with patients, which allowed me to understand the population beyond what the literature could offer. I also tried to invest time early on to communicate the importance of the research – for example through my presence at team meetings and presentations about the rationale for the research to both service users and staff.

Research indicates the importance of involving all stakeholders in the design phases for rare disease research (Rath et al., 2017). This is something I saw the benefit of first-hand and will take forward with me into other projects. Service user and interdisciplinary input – from neurology to nursing and administrative staff – enriched the research design in ways I could not have foreseen. For example, clinicians and service users at the NPC informed the content for the psychoeducation element of the intervention as well as offering important considerations for the overall design through their involvement in the facilitator training sessions and pilot group. My experience with the team and service users provided an understanding of some of the complexities of randomisation in a close-knit, genetically linked population. Issues like familial secrecy and differing levels of awareness and engagement with genetic risk brought nuance that only became visible through real-world contact.

However, while the team's support and belief in the project were motivating, a learning to take forward is that it also made me feel some internal pressure to deliver meaningful results. Discussing this with my supervisor helped me re-centre my perspective and reaffirm the importance of maintaining neutrality and independence, where possible, while also

recognising that complete neutrality is rarely possible in research, as we inevitably bring our own perspectives, experiences, and positions to the work (Berger, 2015).

Methodological Compromises

A second challenge that emerged during the course of this project was striking a balance between adhering to my initial methodological ideals and navigating the practical realities of conducting research in a clinical setting – particularly one involving a rare and under-researched condition.

As a novice researcher, I was committed to conducting the study as rigorously as possible, following recognised best practices. One such aim was to use randomisation in participant allocation to assess the intervention's preliminary effectiveness. However, as the planning progressed, it became clear that strict randomisation was not feasible. Participant requests – for example, to be grouped with or separated from specific family members – along with variable availability and the limited, highly specialised sample pool, made a randomised design impractical.

Similarly, our original exclusion criterion – requiring participants to score above the clinical cut-off on the DASS-21 – had to be revised. A large proportion of interested participants scored in the 'normal' range. This was unexpected, given earlier input from service user focus groups that indicated clear emotional distress and a perceived need for the intervention. It underscored how standardised measures may not fully capture the complexity and nuance of psychological distress, especially within this unique population. The scoping review was particularly helpful in illustrating the fluctuating emotional salience of genetic risk, and how such experiences may not always be reflected in symptom checklists. Ethical considerations also guided this decision; given that participants expressed a strong desire to access the intervention, excluding them solely on the basis of subclinical scores could have

raised concerns about fairness and the withholding of potentially beneficial support (British Psychological Society, 2021).

At the time, I was concerned that these adaptations might weaken our ability to assess the intervention's effectiveness and feared they could undermine the research's credibility. Feasibility studies have historically been critiqued for overlooking methodological rigour or failing to generate data to inform future trials (Shanyinde et al., 2011). However, with the support of my supervisors and after reviewing guidance on conducting feasibility studies – which emphasises that adaptations are often necessary and expected, provided they are transparently reported – I came to see these changes as integral to the learning process (Eldridge et al., 2016). Smith and Thew (2017) note that research does not require complex methodologies or large samples to have scientific value and real-world relevance. This helped shift my perspective: rather than viewing the inability to randomise as a limitation, I began to see it as a key insight into the logistical and ethical complexities of conducting feasibility work in this context. These experiences deepened my appreciation for adaptability in research and highlighted how feasibility studies are not only about testing an intervention, but also about identifying what is and isn't workable in practice.

Conducting research in an emerging area without well-established models was both challenging and energising. With no published psychological intervention studies targeting this population, I often had to make decisions without a clear precedent, which required me to embrace uncertainty and remain open to learning. At times, this felt destabilising, especially when combined with the time pressures of completing a thesis. As someone who tends toward perfectionism, it was difficult to let go of the idea of producing an 'ideal' study and instead focus on what was achievable.

What helped most was following advice from the literature to set clear timelines and monitor progress regularly (Smith & Thew, 2017). Over time, I became more comfortable

with the idea that ‘good enough’ was not only acceptable, but often necessary. I came to appreciate that pragmatism and flexibility are not signs of compromise, but critical skills for or doing meaningful and responsible research.

Evolving as a Researcher

This theme explores how my identity as a researcher evolved over the course of the project and how I navigated the dual roles of clinician and researcher.

The DClinPsy training ethos encourages integration of scientific inquiry with clinical practice, often termed the scientist-practitioner model, but in practice, it is acknowledged that it can be difficult to fully adopt a non-clinical identity (Hays et al., 2016; Jones & Mehr, 2007). This is something which greatly resonated with me, and the project highlighted the tension between these two roles. Trialling an intervention I also facilitated meant I often felt strongly pulled into my clinician identity which comes more naturally to me than my role as researcher.

My instincts to support, contain, and respond to participant needs sometimes conflicted with the structured demands of the research. This conflict was particularly evident during the service user focus groups and participant workshop, where sensitive content often emerged. While I needed to ensure data collection met research aims and that we were able to maintain fidelity across the workshops, I also wanted to respond compassionately and therapeutically. For example, during the focus groups, participants sometimes shared personal experiences in ways that seemed to go beyond the study's scope. This challenged me to find ways to hold space for these moments while still maintaining methodological rigour.

These experiences taught me the importance of being explicit about the boundaries and aims of research from the outset. I also learned that stepping into the researcher role, even when it felt less natural, was not only acceptable but necessary. Hay-Smith et al (2016) introduce the metaphor of “clinical eyes” or “clinical skin” (p.12), which highlights that

clinician-researchers can never be entirely independent of their clinical identity. Similarly, Gardner (1996) highlights how intentionally adopting a clinician-researcher stance can help create a sense of safety and trust, enabling participants to speak more openly and thereby enriching the quality of the data collected I found this a helpful way of considering how to hold this dual identity and to recognise how my clinical skills—such as empathy, sensitivity, and attunement – could enhance my research practice.

My supervisor's guidance was instrumental in helping me notice these dynamics as they arose, for example, using breaks during the workshop to reflect on fidelity and explore any emerging tensions. At times, I had to make on-the-spot decisions about whether to follow the planned structure or respond more flexibly to participant needs. I aimed to do this in a way that remained consistent with ACT principles, even when deviating from the session agenda.

Overall, this experience has deepened my understanding of what it means to be a scientist-practitioner. While I still feel more comfortable in the clinician role, I now have a greater appreciation for research in informing practice and contributing to the evidence base. The gratitude participants expressed for being involved in the research reminded me that this work matters – not only clinically but also in shaping the future of care.

Reflections on the Emotional Challenges of Facilitation

Finally, a major, and somewhat unexpected, theme that emerged from this project was the emotional and cognitive impact of facilitating the intervention itself. While I anticipated that the overall research process would be demanding, I underestimated just how consuming the facilitation role would be. Based on my clinical experience running therapeutic groups, I expected this aspect to feel more familiar and manageable than some of the research elements. However, delivering full-day workshops, in a new format and with a novel client group, presented challenges that went beyond my expectations.

Unlike my typical clinical work, which generally involves shorter 1-1 sessions and provides an opportunity to build relationships with clients over multiple sessions, these workshops required sustained attention and emotional presence across an entire day, with minimal opportunity to step back and process in between. This intensity was amplified by several factors: working with a client group I had no prior clinical experience with; participant distress expressed during discussions; the interactive and dynamic nature of the workshop format; and the central role of the facilitator in actively modelling psychological flexibility and authenticity throughout. In contrast to the more contained role of a therapist, this required me to bring much more of myself into the room – something that could be both connecting and exposing. Corey and Corey (2016) highlight that effective group facilitation requires actively engaging participants, maintaining therapeutic boundaries while navigating complex interpersonal dynamics, and striking the right balance between providing structure and intervening sensitively at the appropriate moments.

This made me consider the importance of building considerations around facilitator needs into intervention planning in addition to participant needs and logistical factors. This was something I had not thought about in the planning stages. One of the workshops coincided with a particularly demanding time in my clinical and personal life, and I found it difficult to switch roles so quickly. If I were to be involved in a similar project again, I would aim to create more space around delivery – for example, building in preparation or recovery time on either side of workshops to allow for greater emotional and cognitive presence. The literature on burnout for psychological therapists may offer some shared learnings also relevant for researchers in clinical settings, including the importance of self-care strategies, effective supervision, seeking peer support and reminding oneself of the meaning and purpose attached to psychological work (Vivolo et al., 2024).

Importantly, things did become easier over time as I became more used to the role of facilitator. Having a co-facilitator was extremely helpful as we were able to divide roles, offer emotional support, and remain attuned to participants' needs in a shared way. For instance, while one of us was presenting, the other could scan the room for signs of distress and respond accordingly. We also prioritised time to debrief after sessions, which helped us reflect, process, and create a sense of psychological closure. This teamwork made a noticeable difference to both the delivery and the experience of the intervention. It made me reflect on how challenging it might be to deliver a group intervention without another clinician present, as well as the importance of building in other forms of reflective support, such as regular supervision that addresses not just research issues but the emotional impact of facilitation.

Ultimately, this part of the project deepened my appreciation for the human demands of delivering psychological interventions and highlighted the need to better integrate facilitator wellbeing into the design and delivery of future research.

Conclusion

Over the course of this project, I experienced a significant shift in my identity as a researcher. Initially, I felt like a novice navigating a highly specialised and emotionally complex topic area. Over time, however, I developed both confidence and competence. In reflecting on the process, what stands out most is the challenge of balancing rigour with pragmatism, and empathy with objectivity. This project has not only strengthened my research skills but also deepened my understanding of what it means to conduct meaningful, ethical, and reflective work within sensitive clinical contexts.

Working in such a novel area brought both uncertainty and opportunity. The scarcity of literature created a steep learning curve but also made space to contribute something original. The rarity of prion diseases and the limited research on those at genetic risk demanded

careful ethical and methodological consideration. Yet, this has ultimately been one of the most rewarding aspects of the work – contributing to an under-researched field and gaining first-hand insight into the complexity of participants' lived experiences and unmet needs.

Importantly, the end of the research process should not mark the end of its impact. After such an intensive piece of work, it can be tempting to draw a line under the project. Yet writing this critical appraisal has reminded me of how much care and thought went into each stage, and importantly, the potential value of the findings. Cooper and Turpin (2007) note that dissemination is often an overlooked stage of the research process. While academic publication remains a key goal, there are many other meaningful ways to share findings – for example, through conferences, team meetings, and directly with patient organisations and service users. As researchers, we have a responsibility to honour the contributions of participants by ensuring that their voices are heard and that the knowledge generated is used to inform and improve care for others living with similar challenges.

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Appendices

Appendix A: PCC Framework for Scoping Review Inclusion and Exclusion Criteria

Category	Criteria
Population	**Include:** Adults (≥18 years) identified as at risk for an ADNC. "At risk" refers to asymptomatic individuals who either tested positive for a pathogenic mutation or have a known family history of the condition but have not undergone testing. **Exclude:** Individuals who have tested negative for the condition and are no longer at risk (unless included as a comparison group); symptomatic individuals or studies not clearly separating symptomatic and asymptomatic participants; conditions that do not follow an autosomal dominant inheritance pattern (e.g., recessive conditions); genetic conditions that are not neurological or affect only the peripheral nervous system (PNS); conditions that are not neurodegenerative or for which a cure is available.
Concept	**Include**: Studies that examine the psychological experience of living at risk for an ADNC as a primary aim or central to the research question, including subjective experiences, psychological outcomes (e.g., anxiety, depression), emotional responses, impact on identity, coping mechanisms, support needs, and strategies for psychological well-being. Eligible studies must directly assess these experiences through quantitative, qualitative, or mixed-method approaches. **Exclude**: Studies focusing primarily on the psychological impact of predictive genetic testing (short- or long-term), or decision-making about whether to undergo testing; studies examining biological, genetic, or clinical

	aspects without a direct focus on the lived psychological experience (e.g., those treating early psychological changes solely as potential preclinical markers of disease); studies where psychological experience is a secondary outcome or not directly assessed.
Context	**Include**: Peer-reviewed journal articles written in English, involving human participants. There is no restriction on publication date. **Exclude**: Grey literature (e.g., conference abstracts, dissertations, preprints), non-English publications, or studies not published in full-text.

Appendix B: Electronic Search Strategy for APA PsycINFO and Ovid MEDLINE

Database	Search Terms	Results
APA PsycInfo <1806 to November 2024 Week 3>	1. (CADASIL or Creutzfeldt-Jakob or Alzheimer* or dementia or Parkinson* or "prion disease" or Ataxia* or Machado-Joseph or Huntington* or leukodystrophy or "Transmissible spongiform encephalopathy" or Gerstmann-Straussler-Scheinker or "fatal familial insomnia" or "motor neuron*" or "Lou Gehrig* disease" or "amyotrophic lateral sclerosis").ab,id,ti. 2. neurodegenerative diseases/ 3. huntingtons disease/ 4. dementia/ 5. (genetic* adj9 risk).ab,id,ti. 6. (familial adj3 risk).ab,id,ti. 7. (inherit* adj3 risk).ab,id,ti. 8. "mutation carrier*".ab,id,ti. 9. (pre-symptomatic or presymptomatic).ab,id,ti. 10. exp At Risk Populations/ 11. (psych* or experience* or self-identity).ab,id,ti. 12. 1 or 2 or 3 or 4 13. 5 or 6 or 7 or 8 or 9 or 10 14. 11 and 12 and 13	840
Ovid MEDLINE <1946 to	1. (CADASIL or Creutzfeldt-Jakob or Alzheimer* or dementia or Parkinson* or "prion disease" or Ataxia* or	1,395

November 22, 2024>	Machado-Joseph or Huntington* or leukodystrophy or "Transmissible spongiform encephalopathy" or Gerstmann-Straussler-Scheinker or "fatal familial insomnia" or "motor neuron*" or "Lou Gehrig* disease" or "amyotrophic lateral sclerosis").ab,kf,ti. 2. Neurodegenerative Diseases/ 3. Dementia/ 4. huntington disease/ or parkinsonian disorders/ 5. (genetic* adj9 risk).ab,kf,ti. 6. (familial adj3 risk).ab,kf,ti. 7. (inherit* adj3 risk).ab,kf,ti. 8. "mutation carrier*".ab,kf,ti. 9. (pre-symptomatic or presymptomatic).ab,kf,ti. 10. Genetic Predisposition to Disease/ 11. (psych* or experience* or self-identity).ab,kf,ti. 12. 1 or 2 or 3 or 4 13. 5 or 6 or 7 or 8 or 9 or 10 14. 11 and 12 and 13

* No date, language, or participant restrictions were applied during the search.

Appendix C: Scoping Review Data Extraction Form Template

Author(s), Year, Country	Aim	Sample	Methodological features	Outcome measures	Data analysis	Key findings	Limitations	Relevance to review

Appendix D: Confirmation of Ethical Approval for Study

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr John Collinge
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04 September 2024

Dear Dr Collinge

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**A longitudinal observation study of all patients diagnosed with or at high risk of developing human prion disease**
IRAS project ID:	**345370**
REC reference:	**24/LO/0510**
Sponsor	**University College London**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **345370**. Please quote this on all correspondence.

Yours sincerely,
Kevin Ahmed

Approvals Manager

Email: approvals@hra.nhs.uk

Copy to: *Miss Elodie Murali,*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
IRAS Application Form [IRAS_Form_10062024]		10 June 2024
Letter from funder [2023 grant award letter]		21 July 2023
Organisation Information Document	1.6	28 February 2024
Other [Amendment Tool]	1.6	06 December 2021
Other [Appendices including questionnaires]		
Other [05MRE0063 SA9 Appendices 2-61_CLEAN COPY]	8.2	12 July 2024
Other [The Research Ethics Committee Feedback]	1.0	02 July 2024
Other [05MRE0063 SA9 Appendices 2-61_CLEAN COPY]	1.0	02 July 2024
Other [CI John C CV]	1.0	12 July 2024
Other [Ethics Feedback 15.08.24]	1.0	14 August 2024
Other [Ethics Feedback 20.08.24]	1.0	21 August 2024
Other [05MRE0063 SA9 Appendices 2-61_Tracked_0.8.2024]	2.0	21 August 2024
Other [Nomimated PIS-CF Appendix 68-69]	3.0	21 August 2024
Other [National Prion Monitoring Cohort Protocol version 8.3 tracked_copy]	8.3	21 August 2024
Participant consent form [MEG CF]	1.1	01 March 2023
Participant consent form	3.0	30 October 2018
Participant consent form [ACT sub-study CF]	1.0	01 March 2024
Participant consent form [Basic consent form]	4.0	01 July 2020
Participant consent form [Control consent form]	3.0	30 October 2018
Participant consent form [CSF CONSENT FORM FOR ASYMPTOMATIC_SYMPTOMATIC IPD PATIENTS]	4.0	19 October 2020
Participant consent form [Investigations Agreement Form]	3.0	30 October 2018
Participant consent form [Investigations consent form]	3.0	30 October 2018
Participant consent form [Patient cf]	5.0	01 July 2020
Participant consent form [Relative_Carer_Consultee Assent Form]	4.0	30 July 2020
Participant consent form [Relative_Welfare Guardian CF]	4.0	01 July 2020
Participant information sheet (PIS) [MEG PIS]	2	17 April 2023
Participant information sheet (PIS) [ACT sub-study PIS]	1.0	01 March 2024
Participant information sheet (PIS) [ACTIGRAPGHY PIS]	3.0	19 October 2020
Participant information sheet (PIS) [Asymptomatic Information Sheet]	4.0	01 July 2020
Participant information sheet (PIS) [CSF SUPPLEMENTARY INFORMATION SHEET]	3.0	02 September 2019
Participant information sheet (PIS) [EEG _ information sheet]	4.0	19 October 2020
Participant information sheet (PIS) [Information Sheet for At Risk Individuals]	4.0	01 July 2020
Participant information sheet (PIS) [Information Sheet for Control Individuals]	3.0	01 July 2020
Participant information sheet (PIS) [Information Sheets_clinical investigation]	4.0	19 October 2020
Participant information sheet (PIS) [Neurophysiological tests]	3.0	19 October 2020
Participant information sheet (PIS) [Patient Information Sheet]	5.0	01 July 2020

Appendix E: Participant Information Sheet

MRC Prion Unit
The National Hospital for Neurology and Neurosurgery
Queen Square
London WC1N 3BG
Tel – 0203 456 7890

Patient Information Sheet

Evaluation of single-session Acceptance and Commitment Therapy (ACT) to support those living at-risk of Prion disease.

(Version 1.0 March 2024)

Invitation

We would like to invite you to take part in a sub-study of the National Prion Monitoring Cohort, which you are enrolled in. This study is a pilot study in which we are exploring whether a single-session Acceptance and Commitment Therapy (ACT) group workshop is a suitable psychological intervention for those living at risk of prion disease. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with a friend, relative or another doctor if you wish. Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of this study?

While those with sporadic prion disease typically have little warning, those with the acquired or inherited forms may spend many years living with the uncertainty of whether they will develop the disease or not. Understandably, this can have a negative impact on psychological wellbeing and increase susceptibility to developing anxiety and depression. Currently, however, there is no published research which investigates psychological support for those living at risk of prion disease.

This study aims to address this by exploring whether a single-session ACT workshop is a suitable intervention for those living at risk of prion disease. The findings will help us to determine whether a full, definitive trial can be delivered which would allow us to assess the effectiveness of the intervention on a much greater scale.

What is Acceptance and Commitment Therapy (ACT)?

ACT is a type of therapy which aims to help people develop psychological flexibility, with a focus on living in line with ones' values rather than trying to get rid of problems. In a single-session form, there is evidence that it is effective in reducing psychological distress for patients with a variety of chronic health conditions. We believe it is a therapy which could be well-suited to capture the diverse difficulties faced by those living at risk of prion disease.

You can find out more about ACT here: https://contextualscience.org/act

Why am I eligible to take part in this study?

We are inviting people who are recruited into the National Prion Monitoring Cohort to take part if they are at risk of inherited (tested or untested) or iatrogenic prion disease.

Do I have to take part?

Your decision to take part is voluntary, and you are under no obligation to do so. This information sheet, which you will be given to keep, describes what the study involves. You will also have the opportunity to ask any questions with one of the Investigators. If you would like to take part in the study, we will ask you to sign a consent form.

You are free to withdraw from the study at any time and do not have to give a reason for doing so. Withdrawal from the study or deciding not to take part will not affect the standard of care you receive or your participation in the National Prion Monitoring Cohort.

What will happen to me if I take part?
If you decide you would like to take part, you will first be asked to fill in a questionnaire which will help us to determine whether you meet requirements to take part in the study. Those who are eligible will be **randomly** assigned to one of two groups: the intervention group or the waitlist group. It is important to note that **everyone** will have the opportunity to receive the intervention; however, those in the intervention group will receive it first.

During the intervention, you will take part in a one-day, face-to-face group ACT workshop at the National Prion Clinic in London. There will be between 5-10 participants in each group. During the workshop you will be invited to participate in various activities and discussions involving paper and pencil tasks or role-play. You will also receive a follow-up phone call approximately a month later to reinforce skills taught and help address any new issues and barriers that have arisen.

At different time points before and after the intervention, you will be emailed or sent by post some questionnaire measures to fill in and return via email or post, regarding your health and well-being and your experience of the workshop. In addition, some participants will be chosen at random to do an interview over the phone about their experience of taking part in the study.

What are the possible disadvantages and risks of taking part?
There are no known risks of receiving this type of therapy. As with any therapeutic treatment, however, some people may engage better than others, and there is no guarantee you will notice an improvement in your psychological wellbeing afterwards. As part of the workshop, we will ask you to think or talk about your current circumstances and some of the things you are finding difficult or distressing in your life – for some people, this can be challenging at first but most people reflect that it is helpful to share these things and say it is useful to learn new skills and techniques to help them cope.

The therapy will be delivered in a group workshop format, and this may mean sharing some personal information with other participants which some people may feel uncomfortable about. To help manage this, we will discuss concerns about privacy at the start and set some clear group rules focused on confidentiality and respecting each other's privacy. Additionally, the workshops will be facilitated by clinicians who have been trained in running this type of group and have the skills and experience to sensitively manage group dynamics and any psychological distress or disruption that arises.

We will require a full day of your time to participate which may mean taking a day off work or from other responsibilities you might have. We will reimburse the costs of travel and/or accommodation (up to £250).

Is there anything else I should know?
You will still continue with the assessments as part of the National Prion Monitoring Cohort, for which you are enrolled. As this study is a sub-study within the Cohort, clinical staff and authorised members of the National Prion Clinic will have access to your data, including clinical assessments and health-related information. With your permission we would like to access your existing data, which will be used strictly in this sub-study.

What are the possible benefits of taking part?
The overall aim of the workshop is to help you create and cultivate a rich, meaningful life by clarifying your values and goals and learning how to let go of the habits holding you back. As part of this, we will be teaching you skills and techniques you can use to develop psychological flexibility and reduce distress. We therefore hope there will be many benefits to taking part both in the immediate and the longer term.

We also hope that the knowledge gained from doing this research will enhance our understanding of how to support those living at risk of prion disease and help us to improve what psychological support is available.

Will my taking part in this study be kept confidential?

Confidentiality measures will be implemented to protect your identity. Your name and contact details will be kept confidential and will not be visible to individuals who do not require access to this information. Instead, your data will be assigned a unique code number to ensure anonymity and maintain confidentiality. We will need to use information from you, and from your medical records for this research project. This information will include your NHS number, name, date of birth and contact details; these details will be stored on secure NHS servers only, or in medical notes stored securely in the National Prion Clinic Office. People will use this information to do the research or to check your records to make sure that the research is being done properly.

We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are my choices about how my information is used?
You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you. If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study. All anonymised data will be securely stored on designated UCL systems.

Where can you find out more about how your information is used?
You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- the leaflet available from www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team
- by sending an email to data-protection@ucl.ac.uk

What will happen to the results of the research study?
This is a research study and we do not know the significance of any findings yet; individualized feedback of results will not be available. Overall results of the study will be written up as part of a research report and can be fed-back once the study is completed. The results of the research may be published in a peer-reviewed scientific journal or presented at UK/international research meetings. You will not be identified in any report or publication.

Who is organising and funding the research?
The CJD Support Network is funding this project as part of its Research Support Research Grant. This study has been reviewed and approved by the London Queen Square Research Ethics Committee (REC).

Contact Information Card
A contact information card has been prepared for distribution upon consent, which contains the clinic and clinicians' contact information.

Contact details

Thank you for taking the time to read this information sheet.
If you have any questions or would like to take part in the study please contact:

Edgar Chan, Consultant Clinical Neuropsychologist
Email: [redacted]

National Prion Clinic, Box 98, National Hospital of Neurology and Neurosurgery
Queen Square, London, WCIN 3BG

Appendix F: Research Study Consent Form

CONSENT FORM

Version 1.0 March 2024
IRAS ID: 345370
COHORT ID:

Title of study – Evaluation of single-session Acceptance and Commitment Therapy (ACT) to support those living at-risk of Prion disease.

Name of Researcher: Edgar Chan

Please initial boxes

1	I confirm that I have read and understood the Patient Information Sheet version 1 (March 2024) for the above study and have had the opportunity to ask questions.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3	I understand that any data obtained as part of the single-session ACT workshop intervention is a gift and will be held and used as described in the accompanying information sheet.	
4	I agree that my data can be shared with the MRC Prion Unit and if shared it will be anonymised and used as part of a research ethics committee approved project.	
5	I understand that sections of any of my medical notes may be looked at by approved members of the study team from the National Prion Clinic, Institute of Neurology, or by regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	
6	In the event that I lose the capacity to make decisions during this study, I agree that my data can still be used for research in prion disease. **(OPTIONAL)**	
7	I agree to take part in the above study.	

_____	_____	_____
Name of patient	Date	Signature
_____	_____	_____
Name of Researcher	Date	Signature

Appendix G: ACT Workshop for Prion Agenda

(Removed from copy for reasons relating to copyright)

Appendix H: ACT Workshop Participant Manual

(Removed from copy for reasons relating to copyright)

Appendix I: Booster Session – Standardised List of Discussion Topics

(Removed from copy for reasons relating to copyright)

Appendix J: ACT Workshops Fidelity Checklist

(Removed from copy for reasons relating to copyright)

Appendix K: Post Workshop Questionnaire

Post workshop questionnaire

COHORT ID NUMBER:

General questions

Have you had any form of psychological therapy before (either 1-1 or in a group)?

☐ Yes - I've had ACT before ☐ Yes - but not ACT ☐ No ☐ Would rather not say

If you answered yes to the above, how recently was this?

☐ Currently ☐ Less than a year ago ☐ 1-2 years ago ☐ 2-5 years ago ☐ Over 5 years ago

If you answered yes to the above, how many sessions did you have in total?

☐ 1 session ☐ 2-6 sessions ☐ 6-8 sessions ☐ 8-12 sessions ☐ Over 12 sessions

Did you watch the pre-workshop educational video?

☐ Yes, all of it ☐ Yes, some of it ☐ No, didn't think it would be helpful ☐ No, didn't have time

Workshop feedback

How useful did you find taking part in the workshop?

☐ 1 - not useful at all ☐ 2- not that useful ☐ 3 - no opinion ☐ 4 - useful ☐ 5 - very useful

Did you like or dislike the workshop?

☐ 1 - strongly dislike ☐ 2- dislike ☐ 3 - no opinion ☐ 4 - like ☐ 5 - strongly like

How much effort did it take to engage with the workshop?

☐ 1 - no effort ☐ 2- a little effort ☐ 3 - no opinion ☐ 4 - a lot of effort ☐ 5 - huge effort

There are moral or ethical consequences for people to take part in the workshop

☐ 1 - strongly disagree ☐ 2- disagree ☐ 3 - no opinion ☐ 4 - agree ☐ 5 - strongly agree

The workshop has improved my ability to manage living at risk

☐ 1 - strongly disagree ☐ 2- disagree ☐ 3 - no opinion ☐ 4 - agree ☐ 5 - strongly agree

How confident did you feel about taking part in the workshop?

☐ 1 - very unconfident ☐ 2- unconfident ☐ 3 - no opinion ☐ 4 - confident ☐ 5 - very confident

Taking part in the workshop interfered with my other priorities

☐ 1 - strongly disagree ☐ 2- disagree ☐ 3 - no opinion ☐ 4 - agree ☐ 5 - strongly agree

Overall, how acceptable was the workshop to you?

☐ 1 - completely unacceptable ☐ 2- unacceptable ☐ 3 - no opinion ☐ 4 - acceptable ☐ 5 - completely acceptable

Is there anything else you would like to add about your experience of taking part?

Thank you for taking the time to participate in today's workshop. We hope you found it a valuable experience and welcome any further feedback you would like to provide over email or in person.

Appendix L: Structured Interview Guide/Open-Ended Questions

1. **Did the workshop meet your expectations – why/why not?**

2. **What was your overall impression of the workshop and the 2-4 week booster call?**

Prompts: What did you think about the workshop/call length, number of participants, content and amount of information presented?

3. **Are there any ways in which you think the workshop and/or booster call could be improved?**

4. **What exercise/skills/strategies did you find most helpful and why?**

5. **What exercise/skills/strategies did you find least helpful and why?**

6. **Did you think the ACT workshop was appropriate for you/those living at risk of prion disease? Why / Why not?**

7. **What did you think of the workshop manual? Have you used it since attending?**

8. **Is there anything else you would like to add about your experience of taking part in the workshop?**

Appendix M: ACT Adherence Coding Sheet for Booster Sessions

0 = No evidence of ACT skill use
The participant did not mention using or attempting to use any ACT-based strategies or principles introduced during the workshop.

1 = Minimal or inconsistent use of ACT principles
The participant mentioned ACT skills or ideas but described little or only occasional use. Application appeared sporadic, superficial, or reactive rather than intentional or sustained.

2 = Moderate and somewhat consistent use of ACT principles
The participant reported using one or more ACT skills in daily life with some regularity. However, use appeared limited to specific situations or contexts, with little evidence of applying skills across different areas of life.

3 = Frequent and flexible use of ACT principles
The participant described actively and deliberately using a range of ACT skills in various situations. Responses reflected both a solid understanding of the principles and a clear effort to apply them in multiple areas of daily life (e.g., work, relationships, personal challenges).