CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER: P1V-GAINS-IN01

STUDY TITLE: A randomised optimisation study of a brief digital imagery-competing task intervention to support NHS ICU staff experiencing intrusive memories of traumatic events from working in the COVID-19 pandemic

Final Protocol Date:	11 MAR 2022
Sponsor:	P1vital Products Ltd, Manor House, Howbery Park, Wallingford, Oxfordshire, OX10 8BA

SIGNATURE PAGE

SPONSOR

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding regulatory guidelines and confidentiality.

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Protocol Synopsis

Study Title: A randomised optimisation study of a brief digital imagery-competing task intervention to support NHS ICU staff experiencing intrusive memories of traumatic events from working in the COVID-19 pandemic.
Short Study Title: A brief GAmeplay Intervention for NHS ICU Staff affected by COVID-19 trauma (GAINS Study)
Chief Investigator: Dr Lalitha Iyadurai
Study Centre(s): Study will be completed remotely in locations of participant's choosing with internet accessibility
Primary Objective: • To determine if immediate access to the intervention plus symptom monitoring for 4 weeks (immediate intervention arm), compared to usual care for 4 weeks (delayed intervention arm), can reduce the number of intrusive memories in week 4 (i.e. between-groups comparison). **Secondary Objectives:** • To determine if access to the intervention plus symptom monitoring for 4 weeks can reduce the number of intrusive memories from run-in week (pre-intervention) to week 4 (post intervention; within-group comparison in the immediate intervention arm) and from week 4 (pre intervention) to week 8 (post intervention; within-group comparison in the delayed intervention arm) • To determine if immediate access to the intervention plus symptom monitoring for 4 weeks (immediate intervention arm), compared to usual care for 4 weeks (delayed intervention arm), can reduce intrusive memory ratings of distress and disruption to concentration/functioning; symptoms of post-traumatic stress, anxiety, depression and insomnia; sickness absence; burnout; intention to leave job; and improve work engagement, functioning and quality of life at 4 weeks (i.e. between-groups comparison). • To determine if access to the intervention plus symptom monitoring for 4 weeks can reduce intrusive memory ratings of distress and disruption to concentration/functioning; symptoms of post-traumatic stress, anxiety, depression and insomnia; sickness absence; burnout; intention to leave job; and improve work engagement, functioning and quality of life from baseline (pre intervention) to 4 and 8 weeks (post intervention; within-group comparison in the immediate intervention arm) and from 4 weeks (pre intervention) to 8 weeks (post intervention; within-group comparison in the delayed intervention arm). **Tertiary Objectives:** • To assess support (from managers and from family/friends), new stressful/traumatic events, new treatments, changes to work • To obtain feasibility data to improve the intervention implementation. • To assess the acceptability and perceived value of the intervention from participants to optimise the intervention implementation. • To assess the guidance given by the expert researchers to participants to explain how to use the intervention, in order to identify ways to train non-expert researchers to give guidance.

• To assess the guidance given by both expert and non-expert researchers to identify ways to digitise such guidance to establish a fully self-guided version of the intervention.
Hypothesis and Brief Rationale: The primary hypothesis is that participants in the immediate intervention arm, compared to the delayed intervention arm, will have fewer intrusive memories in week 4 (between-groups comparison).
Study Design: This optimisation study uses a two-arm, parallel-group, randomised controlled trial. The study's randomisation method allocates participants using a 1:1 overall ratio to one of two arms: Immediate intervention arm = immediate access to the brief digital imagery-competing task intervention plus symptom monitoring for 4 weeks Delayed intervention arm = usual care for 4 weeks followed by access to the intervention plus symptom monitoring for 4 weeks
Study Period: Each participant will be in the study for a total of up to 17 weeks. There will be virtual visits (i.e., audio or video calls between participant and researcher) at screening, on first intervention day, for optional qualitative interview, and to provide support with additional intervention sessions or assist the participant (e.g., with outcome completion) when appropriate. Remote participant assessments (i.e., typically without researcher; online questionnaires only) will take place at Baseline, 4 and 8 weeks. Total duration of the study from first participant enrolment to last participant completing the study is expected to last approximately 9 months, but will depend on the number enrolled.
Number of Participants: The study will enrol up to approximately 150 participants, 75 per study arm.
Main Entry Criteria: Main Inclusion Criteria: • Aged 18 or above. • Able to read, write and speak in English. • Worked in a clinical role in an NHS Intensive Care Unit or equivalent during the COVID-19 pandemic (e.g. as a member of ICU staff or deployed to work in the ICU during the pandemic). • Experienced at least one traumatic event related to their work during the COVID-19 pandemic, meeting criterion A of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria for Post-Traumatic Stress Disorder (PTSD): "exposure to actual or threatened death, serious injury, or sexual violence" by "directly experiencing the traumatic event(s)" or "witnessing, in person, the event(s) as it occurred to others". • Experience intrusive memories of the traumatic event(s). • Experienced at least three intrusive memories in the week prior to screening. • Have internet access. • Willing and able to provide informed consent and complete study procedures (including briefly listing their intrusive memories (without going into any detail), and playing the computer game Tetris® with particular mental rotation instructions, and completing an online intrusive memory diary).

- Willing and able to be contacted by the research team during the study period.

Main Exclusion Criteria:

Have fewer than three intrusive memories during the run-in week. We will not exclude those undergoing other treatment for PTSD or its symptoms, so the study is as inclusive as possible to meet the challenges ICU staff are facing during the COVID-19 pandemic.

Study Intervention:

This brief imagery-competing digital task intervention consists of a brief reminder cue to a specific intrusive memory, followed by playing the computer game Tetris® for 20 minutes with instructions to use mental rotation during game play. The study team will provide a single training session on completing the intervention for the first time (guided session). The intervention can then be repeated for other intrusive memories. Participants will learn to complete the intervention in the initial guided session with the help of a researcher, and thereafter use it self-guided for other existing intrusive memories or if intrusive memories from a new trauma arise (with the option for researcher support). The intrusive memory diary (based on e.g., Holmes et al., 2009; Iyadurai et al., 2018; Kanstrup, Singh et al., 2021; Kubickova et al., in prep) helps to indicate when they might benefit from repeating the intervention.

Outline of Study:

The study is divided into approximately a 1-5 week screening period including one week run-in period to determine eligibility prior to randomisation followed by approximately 8 weeks in the study period and 2 weeks optional, qualitative interview period.

Participants will be recruited through the Intensive Care Society network membership and existing social media followers supplemented by targeted advertisements in social media (e.g. Facebook, Twitter).

Those who are interested in taking part in the study will be asked to complete a brief online eligibility questionnaire anonymously, which can be accessed on the study website. Participants will be asked to give online consent before completing the questionnaire. Those who meet all the inclusion criteria will be asked to provide their contact details (name, telephone number and email address). A researcher will then arrange a time to contact them by phone or video call to obtain informed consent and go through the study inclusion and exclusion criteria.

All participants will be asked to complete a daily online intrusive memory diary for a run-in period of one week to record a simple count of the number of intrusive memories they have each day using a secure web-based clinical research system, P1vital® electronic patient reported outcome (ePRO) system. Those meeting the study eligibility criteria will then be sent a link to complete baseline questionnaires using ePRO. After completing baseline questionnaires, participants will be randomised by ePRO to receive either the immediate intervention arm or the delayed intervention arm using a 1:1 overall ratio. After randomisation, participants will be sent information explaining what will happen next in the study. This information will differ according to whether they have been allocated to the immediate intervention or delayed intervention arm. Note: to minimise expectation bias, participants are not told that the study has two arms or to which arm they have been assigned; participants are informed during the consent process that they will have access to an online intervention for 4 weeks ‘at some point’ within an 8-week period.

- Participants in the immediate intervention arm will be contacted immediately by a researcher to arrange a video call to go through the brief digital intervention for the first time with researcher support (the guided session: Day 1). The brief digital intervention is a c. 30-minute, single session task completed by the participant on their smart phone or other internet enabled device delivered on a secure web platform

used for clinical self-management of health in general practice (i-spero®). Participants in this arm will have continuous access to the intervention over the next 4 weeks (Day 1-28) and can use the intervention either on their own or with the option of researcher support. As part of the intervention, participants complete a daily record of their intrusive memories in i-spero® to identify which intrusive memories they have had, and therefore which to target with the intervention. In week 4 (Day 22-28), they will be asked to complete a daily intrusive memory diary and intrusive memory rating questionnaire in ePRO (identical to the run-in week) to assess how many intrusive memories they had each day.

- Participants in the delayed intervention arm will be asked to complete the online intrusive memory diary and intrusive memory rating questionnaire using ePRO during week 4 (Day 22 to 28), to assess how many intrusive memories they had each day. The online intrusive memory diary completed during week 4 will be the same as the intrusive memory diary completed by all participants in the run-in week. After these first 4 weeks, they will be contacted by a researcher to arrange a video call to go through the brief digital intervention for the first time (as in the immediate intervention group, i.e. the guided session: Day 29+7 days[1]). Participants in the delayed intervention arm will have continuous access to the intervention over the next 4 weeks (Day 29 to 56+7 days) and can use the intervention either on their own or with the option of researcher support. As part of the intervention, participants complete a daily record of their intrusive memories to identify which intrusive memories they have had, and therefore which to target with the intervention. In week 8 (Day 50 to 56 +7), they will be asked to complete a daily intrusive memory diary and intrusive memory rating in ePRO (identical to the run-in week) to assess how many intrusive memories they had each day.

Participants in both arms will be asked to complete outcome questionnaires using ePRO at 4 weeks (Day 28) and 8 weeks (Day 56). They will also be asked to complete an online feedback questionnaire about their experience of using the intervention and they will be given the option of completing a qualitative interview with a researcher via audio or video call. This will be completed after week 4 (Day 28) for participants in the immediate intervention arm and after week 8 (Day 56+7 days) for participants in the delayed intervention arm.

Note: Day 1 in the immediate intervention group is defined as the day on which the participant completes the first intervention session with researcher support (guided session). The timing of this first intervention session post randomisation may vary slightly from participant to participant in the intervention arm. Day 1 for participants in the delayed intervention arm will be paired to the timing of Day 1 for participants in the immediate intervention arm, so that the timing of the primary outcome assessment post randomisation will be approximately equal between the two groups.

Endpoints / Outcome Measures

Primary Endpoint:

- Number of intrusive memories of traumatic events recorded by participants in a brief daily online intrusive memory diary for 7 days during week 4 (i.e. from Day 22 to 28 post first intervention session in immediate intervention arm/equivalent timeframe in delayed intervention arm). Analysed as between-group comparison (immediate

[1] A 7-day window, denoted by "+7 days", is anticipated to allow time to arrange the first intervention session with participants in the delayed intervention arm.

intervention arm vs. the delayed intervention arm) controlling for the number of intrusive memories during the run-in week.

Secondary Endpoints:

- Number of intrusive memories recorded by participants in a brief daily online intrusive memory diary for 7 days during the run-in week (pre intervention) and week 4 (Day 22 to 28) in the immediate intervention arm; and during week 4 (Day 22 to 28) and week 8 (Day 50 to 56+7 days) in the delayed intervention arm (i.e. within-group comparisons).
- Intrusive memory ratings (distress, disruption to concentration/functioning: how much and how), Impact of Event Scale-Revised (IES-R), PTSD Checklist for DSM-5 (PCL-5) 4-item, Generalised Anxiety Disorder-2-item questionnaire (GAD-2), Patient Health Questionnaire-2-item version (PHQ-2), Sleep Condition Indicator (SCI-08), Physiological Outcome Profile Questionnaire (PSYCHLOPS), World Health Organization Disability Assessment Schedule (WHODAS), 5-level EQ-5D (EQ-5D-5L), Number of sick days, Scale of Work Engagement and Burnout (SWEBO), Intention to leave job at 4 weeks (i.e. Day 28 post first intervention session in immediate intervention arm/equivalent timeframe in delayed intervention arm) in the immediate intervention arm vs. the delayed intervention arm (i.e. between-groups comparison).
- Intrusive memory ratings (distress, disruption to concentration/functioning: how much and how), Impact of Event Scale-Revised (IES-R), PTSD Checklist for DSM-5 (PCL-5) 4-item, Generalised Anxiety Disorder-2-item questionnaire (GAD-2), Patient Health Questionnaire-2-item version (PHQ-2), Sleep Condition Indicator (SCI-08), Physiological Outcome Profile Questionnaire (PSYCHLOPS), World Health Organization Disability Assessment Schedule (WHODAS), 5-level EQ-5D (EQ-5D-5L), Number of sick days, Scale of Work Engagement and Burnout (SWEBO), Intention to leave job at baseline, 4 weeks (Day 28) and 8 weeks (Day 56) in the immediate intervention arm; and at 4 weeks (Day 28) and 8 weeks (Day 56+7 days) in the delayed intervention arm (i.e. within-group comparisons).

Tertiary Endpoint

- 8-item questionnaire (changes to health and work) at 4 weeks (Day 28) and 8 weeks (Day 56) (both arms).
- Rates of recruitment, intervention use/adherence, outcome measure completion and participant attrition.
- Feedback questionnaire at 4 weeks post first intervention session in both arms (i.e. Day 28 in the immediate intervention arm and Day 56+7 days in the delayed intervention arm).
- Optional qualitative interview at 4 to 6 weeks post first intervention session in both arms (i.e. Day 29+14 days in the immediate intervention arm and Day 57+14 days in the delayed intervention arm).
- Optional qualitative interview information about guidance given by the expert/non expert researchers to help participants to learn how to use the intervention.

Refer to section 5.7 for specific timings of assessments by day.

Statistical Methodology:

Bayesian and frequentist analyses will be used for statistical inference. The Bayesian approach will be used throughout data collection to inform on study design. Standard (frequentist) statistical approaches will be used at the end of the study to analyse the primary, secondary and tertiary data.

Study Design Analysis

- Ongoing sequential analysis using Bayesian statistical approaches will be used to evaluate the study design based on the primary outcome (difference in the number of intrusive memories in week 4 for groups of participants. The analysis will control for the number of intrusive memories during the run-in week.

End of Study Analysis

Primary Analysis

- A between-groups analysis will be used to test the difference in the number of intrusive memories in week 4 (i.e. from Day 22 to 28) between the immediate intervention and delayed intervention groups. The analysis will control for the number of intrusive memories during the run-in week.

Secondary Analysis

- A within-group analysis will be used to test the change in the number of intrusive memories from the run-in week to week 4 (Day 22 to 28) in the immediate intervention group.
- A within-group analysis will be used to test the change in the number of intrusive memories from week 4 (Day 22 to 28) to week 8 (Day 50 to 56+7 days) in the delayed intervention group.
- Between-groups analyses will be used to test for differences in other secondary outcomes at 4 weeks (Day 28) between the immediate intervention and delayed intervention groups: intrusive memory ratings of distress and disruption to concentration / functioning; symptoms of post-traumatic stress, anxiety, depression and insomnia; sickness absence; work engagement and burnout; intention to leave job; functioning and quality of life.
- Within-group analyses will be used to test the change in other secondary outcomes (listed above) from baseline to 4 weeks (Day 28) in the immediate intervention group.
- Within-group analyses will be used to test the change in other secondary outcomes (listed above) from 4 weeks (Day 28) to 8 weeks (Day 56) in the delayed intervention group.
- Within-group analyses will be used to test if changes in secondary outcome measures are maintained at 8 weeks (Day 56) post intervention onset in the immediate intervention arm.

Tertiary Analyses

- Descriptive statistics will be used to summarise support from managers and friends family and changes to health and work in the two groups.
- Descriptive statistics will be used to summarise rates of recruitment, intervention use/adherence, outcome measure completion and participant attrition.
- Descriptive statistics will be used to summarise quantitative data regarding intervention acceptability (feedback questionnaire)
- Qualitative interview data will be thematically analysed using an inductive thematic, constant comparison approach based on grounded theory (Glaser and Strauss 1967).

References:

Holmes, E. A., James, E. L., Coode-Bate, T., & Deeprose, C. (2009). Can playing the computer game "Tetris" reduce the build-up of flashbacks for trauma? A proposal from cognitive science. PLoS ONE, 4(1), e4153.

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after trauma via a brief intervention involving Tetris computer game play in the emergency department: a proof-of-concept randomized controlled trial. Molecular Psychiatry. 23(3), 674-682.

Kanstrup, M.*, Singh, L.*, Göransson, K., Widoff, J., Taylor, R., Iyadurai, L., Moulds, M. & Holmes, E. A. (2021). Preventing intrusive memories after trauma via a simple cognitive intervention in the hospital emergency department: An explorative randomised controlled pilot trial. *Translational Psychiatry*, *11*(30). https://doi.org/10.1038/s41398-020-01124-6. *co-shared first authorship

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List of Abbreviations

AE	Adverse Event
COVID-19	Coronavirus Disease 2019
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
GAD-2	Generalised Anxiety Disorder – 2-item questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
ePRO	Electronic Patient Reported Outcomes
EQ-5D-5L	5-level EQ-5D
ICF	Informed Consent Form
ICU	Intensive Care Unit
IES-R	Impact of Event Scale-Revised
NHS	National Health Service
PCL-5	PTSD Checklist for DSM-5
PHQ-2	Patient Health Questionnaire – 2-item version
PI	Principal Investigator
PIS	Participant Information Sheet
PSYCHLOPS	Psychological Outcome Profiles Questionnaire
PTSD	Post-traumatic Stress Disorder
REC	Research Ethics Committee
SCI	Sleep Condition Indicator
SWEBO	Scale of Work Engagement and Burnout
WHO	World Health Organization
WHODAS	World Health Organization Disability Assessment Schedule

1.0 Introduction and Rationale

1.1 Background

1.1.1 The mental health impact of covid-19 trauma on health care staff

The mental health of frontline healthcare staff who are delivering care to COVID-19 patients is a major priority internationally (Holmes et al., 2020), for two reasons:

1. Frontline healthcare staff are at elevated risk of post-traumatic stress disorder (PTSD) and other mental health symptoms due to increased exposure to occupational trauma and require prompt access to effective interventions.
2. Retaining healthcare staff in their jobs and preventing work dropout is necessary for delivering critical care to COVID-19 patients.

During the COVID-19 pandemic, frontline healthcare staff are experiencing extreme exposure to potentially traumatic events, e.g. traumatic or tragic death of a patient (Adriaenssens et al., 2012; Jonsson & Segesten, 2003; Laposa et al., 2003; Michael & Jenkins, 2001), or heightened risk of infection (Kang et al., 2020; Zhang et al., 2020).

After a trauma, it is common to experience intrusive memories (or “flashbacks”) of the event. Even before COVID-19, 65% of emergency nurses reported having intrusive memories of work-related traumatic events (Kleim et al., 2015) – emotional, intrusive and primarily visual memories of the traumatic event that pop suddenly into mind. For some individuals, intrusive memories persist, and become a core symptom of post-traumatic stress disorder (PTSD) (American Psychiatric Association, 2013).

Around 40% of healthcare staff in UK hospitals reported a level of symptoms consistent with a diagnosis of PTSD as of June/July 2020 (Greenberg et al., 2021)- five times higher than in 2015 (Colville et al., 2015). Of this sample of almost 3000 respondents, approximately one quarter report “Repeated, disturbing memories, thoughts of images related to the current pandemic” (i.e., intrusive memories) have been bothersome (scores of 3=moderately to 5=extremely on the PCL-6; (Lang et al., 2012) Greenberg on our Expert Advisory Panel, personal communication (Greenberg, 2021)).

Recent studies from China report that between 24% and 35% of healthcare workers reported PTSD symptoms during the COVID-19 pandemic (Tan et al., 2020; Lai et al., 2020; Kang et al., 2020).

PTSD has a major impact on an individual’s functioning and incurs great cost for both the individual and society. PTSD symptoms can impair work performance: 27% of healthcare workers who reported PTSD symptoms said they interfered with their work functioning (Laposa & Alden, 2003) and 20% considered changing their job (Laposa, Alden & Fullerton, 2003). Mental health problems are the leading cause of sickness absence in the NHS (NHS Digital, 2020).

1.2 Rationale

1.2.1 Limitation to existing interventions after trauma

Whilst there are effective treatments for PTSD, such as talking therapies like trauma-focused cognitive behavioural therapy (NICE, 2018), uptake in frontline staff is limited by difficulty finding time to attend fixed therapy sessions and mental health stigma. Moreover, we lack evidence-based interventions to target sub-clinical symptoms and prevent full-blown PTSD from developing - which is critical to keeping frontline staff working well. We urgently need psychological interventions for healthcare staff that are brief, remotely-delivered (digital), low stigma and scalable.

1.2.2 A mechanism-based intervention to target intrusive memories of trauma

Intrusive memories of trauma may be a potential target for early and preventative interventions post-trauma (Iyadurai et al., 2019). Intrusive memories are centrally linked to other symptoms of the disorder, both at an early and later period post-trauma (Bryant et al, 2017). This has led to the suggestion that targeting intrusive memories may prevent PTSD from developing (McNally, 2017).

Almost two decades of laboratory and clinical studies within Prof Holmes' research group has led to the development of a brief mechanism-driven behavioural intervention to reduce intrusive trauma memories (e.g. Holmes, James, Coode-Bate, & Deeprose, 2009; James et al., 2015).

This brief imagery-competing task intervention consists of a brief reminder cue to orient to the traumatic event, followed by playing the computer game Tetris for 20 minutes with instructions to use mental rotation during game play. The principles of the intervention are informed by the (neuro)science of memory consolidation and cognitive task interference. The hypothesis is that the memory consolidation process of a traumatic event can be disrupted by engaging in visuospatial demanding tasks, e.g. Tetris, and reduce the frequency of the intrusive memories. However, the ability to voluntarily recall the memories does not appear to be affected in laboratory studies.

1.2.3 Clinical translation and application

The intervention is thought to be effective across different types of traumatic events. A number of pilot and proof-of-concept clinical studies have been carried out – three randomised controlled trials and three case series studies. An initial randomised controlled trial compared the intervention to usual care in woman who had an emergency caesarean section (traumatic childbirth). The results showed that the frequency of intrusive memories decreased during the following week for the intervention group in comparison to the control group (Horsch et al, 2017). Similar results were found in a randomised controlled study with participants admitted to a UK emergency department after a traumatic motor vehicle accident. Those who received the intervention,

compared to an attention-placebo control, reported fewer intrusive memories over the next week (Iyadurai et al., 2018). In a pilot replication trial in a Swedish emergency department, reduction in intrusive memory frequency was maintained (and in fact even greater) at 5 weeks post intervention (Kanstrup, Singh et al., 2021). In all of these trials, feedback from participants indicated that the intervention was acceptable. Finally, the intervention has also been found to reduce intrusive memories in case series studies with patients with chronic PTSD (Kessler et al, 2018), refugees (Kanstrup et al., 2020), and most recently NHS staff exposed to work-related trauma including during the COVID-19 pandemic (Kubickova et al., in prep).

Our game-based intervention is an 'early intervention' that aims to reduce and prevent the recurrence of intrusive memories during the COVID-19 pandemic. The intervention can be delivered within the timeframes of early prevention (within 1 month after the traumatic event), early preventative treatment (1-3 months after the event), delayed preventative treatment (>3 months after the event), or during ongoing trauma exposure (NICE evidence reviews for PTSD prevention, 2018). Within the NICE evidence reviews for PTSD prevention (2018), the intervention would be considered as self-help with or without support.

1.2.4 Aims of the current study

The current study aims to investigate if the effects of the intervention a) extend to ICU staff who have experienced work-related traumatic events during the COVID-19 pandemic, and b) impact key secondary outcomes such as other mental health symptoms, work functioning, sickness absence and intention to leave the job.

The intervention holds particular promise for overcoming some of the challenges of implementing mental health interventions for healthcare staff as it is brief (one guided intervention session of approximately 30 minutes), can be used flexibly in different locations (e.g. on a smartphone during a commute), and is non-stigmatising (involves a digital task including a computer game rather than talking to a trained therapist). Participants can then use it self-guided for additional different intrusive memories they may be experiencing. It can also be delivered following each new traumatic event, and for new intrusive memories as they arise, so is well-suited for healthcare staff facing repeated or ongoing trauma in their jobs during the pandemic. Participants do not need to talk about the traumatic event in detail, which minimises distress.

Results of the study will be relevant globally to healthcare staff affected by traumatic events during the COVID-19 pandemic.

1.2.5 Main research questions

1. Can a brief digital imagery-competing task intervention for national health service (NHS) intensive care unit (ICU) staff who have experienced work-related traumatic events during COVID-19:

a) Reduce the number of intrusive memories in week 4 (Day 22 to D28) (primary outcome)?

b) Reduce symptoms of PTSD, anxiety, depression and insomnia (secondary outcomes)?

c) Improve work functioning and engagement, and reduce sickness absence, burnout and intention to leave the profession (secondary outcomes)?

2. Is the intervention feasible and acceptable to NHS ICU staff? (tertiary outcomes)

3. How can we optimise the intervention for guided delivery by non-expert researchers and inform non-guided delivery? (tertiary outcomes)

1.3 Risks and benefits

1.3.1 Benefits

The study holds the following potential benefits to NHS ICU staff and COVID-19/other patients:

1. Immediate clinical benefit to NHS ICU staff participants, by reducing distressing intrusive memories and other mental health symptoms.

2. Immediate benefit to staff job performance and delivery of care to COVID-19/other patients, by reducing disruption to concentration and work performance caused by intrusive memories.

3. Longer-term/preventative impact on staff participants' mental health, by reducing the persistence of PTSD symptoms and other mental health symptoms.

4. Longer-term impact on staff sickness absence, burnout and intention to leave the job.

5. Longer-term impact on the delivery of care to COVID-19/other patients, due to improved staff retention.

Previous studies show that participants rate the intervention as easy, helpful, minimally distressing/burdensome and acceptable (Horsch et al, 2017; Iyadurai et al, 2018; Kanstrup, Singh et al, 2021). Moreover, participants reported that the intervention took their mind off the traumatic event (e.g. Iyadurai et al, 2018) and was fun and relaxing (Kanstrup, Singh et al, 2021). All participants will be given information on how to seek help for any ongoing mental health concerns at the end of the study, and individuals who are not eligible for the study will be signposted to NHS/Every Mind Matters and other support websites.

1.3.2 Risks and measures to minimise them

The study has no anticipated long-term risks to participants, and no adverse events related to study procedures have been reported by participants in previous trials of the intervention (Horsch et al., 2017; Iyadurai et al., 2018; Kanstrup, Singh et al., 2021).

However, the study procedures may be associated with the following risks and measures to minimise each risk are also described:

1. Briefly listing image-based intrusive memories of traumatic events and bringing them to mind as part of the intervention (memory reminder) may be unpleasant or distressing for some participants.

This procedure has been tested in several previous studies (Iyadurai et al., 2018; Kanstrup et al, 2020; Kanstrup, Singh et al., 2021) with no adverse consequences. The procedure is very brief, and participants are only asked to write a few words for each intrusion, before moving on quickly to the next. Participants are only asked to bring to mind the image very briefly, before moving immediately on to playing Tetris. Participants are not required to recall or describe the traumatic event(s) in detail.

2. Some participants may find playing the computer game Tetris difficult or stressful.

Tetris is a simple and popular computer game, and whilst most participants in previous studies have reported finding it fun and distracting, participants occasionally find it difficult or stressful. All participants will be given instructions on how to play Tetris, and in this study the difficulty of the game adapts to the skill of the player. The researcher will be present to help the participant the first time they do the intervention. Many healthcare staff already use computer games for distraction and recreation (BBC News, 2020).

3. Completing outcome measures may be perceived as burdensome by some participants.

We have tried to minimise participant burden by limiting the number of outcome measures, and wherever possible using shortened versions of measures (e.g. 4-item PTSD Checklist for DSM-5). We have selected measures with the specific needs and demands of healthcare staff in mind. All outcome measures will be administered online, meaning that participants can complete them at a time and place that suits them.

4. Some staff who do not meet the eligibility criteria may still be experiencing difficulties.

To address this, we will ensure that all potential participants who do not meet the initial screening criteria will be signposted to the NHS/Every Mind Matters and other support website.

The research team includes qualified Clinical Psychologists and Psychiatrists with extensive experience in running clinical research studies in mental health. These include previous studies testing this intervention, trials of other digital mental health interventions, and studies with healthcare staff and students. The study has been designed in line with Good Clinical Practice (GCP) guidance, and all investigators are GCP trained. Dr Lalitha Iyadurai and Professor Emily Holmes (clinical psychologists) have expertise in treating

traumatised individuals and will be involved in the training and monitoring of the study team.

2.0 Study Objectives

2.1 Primary Objective

- To determine if immediate access to the intervention plus symptom monitoring for 4 weeks (immediate intervention arm), compared to usual care for 4 weeks (delayed intervention arm), can reduce the number of intrusive memories in week 4 (i.e. between-groups comparison).

2.2 Secondary Objectives

- To determine if access to the intervention plus symptom monitoring for 4 weeks can reduce the number of intrusive memories from run-in week (pre-intervention) to week 4 (post intervention; within-group comparison in the immediate intervention arm) and from week 4 (pre intervention) to week 8 (post intervention; within-group comparison in the delayed intervention arm)

- To determine if immediate access to the intervention plus symptom monitoring for 4 weeks (immediate intervention arm), compared to usual care for 4 weeks (delayed intervention arm), can reduce intrusive memory ratings of distress and disruption to concentration/functioning; symptoms of post-traumatic stress, anxiety, depression and insomnia; sickness absence; burnout; intention to leave job; and improve work engagement, functioning and quality of life at 4 weeks(i.e. between-groups comparison).

- To determine if access to the intervention plus symptom monitoring for 4 weeks, can reduce intrusive memory ratings of distress and disruption to concentration/functioning; symptoms of post-traumatic stress, anxiety, depression and insomnia; sickness absence; burnout; intention to leave job; and improve work engagement, functioning and quality of life from baseline (pre intervention) to 4 and 8 weeks (post intervention; within-group comparison in the immediate intervention arm) and from 4 weeks (pre intervention) to 8 weeks (post intervention; within-group comparison in the delayed intervention arm).

2.3 Tertiary Objectives

- To assess support (from managers and family/friends), new stressful/traumatic events, new treatments, changes to work.

- To obtain feasibility data to improve the intervention implementation.

- To assess the acceptability and perceived value of the intervention from participants to optimise the intervention implementation.

- To assess the guidance given by the expert researchers to participants to explain how to use the intervention, in order to identify ways to train non-expert researchers to give guidance.

- To assess the guidance given by both expert and non-expert researcher to identify ways to digitise such guidance to establish a fully self-guided version of the intervention.

Primary, secondary, tertiary endpoints and outcome measures are outlined in section 9 of the protocol.

3.0 Study Design

3.1 Overview

The study is a randomised optimisation study of a brief digital imagery-competing task intervention to support NHS ICU staff experiencing intrusive memories of traumatic events from working in the COVID-19 pandemic.

Participants will be randomised to one of two study arms:

The Immediate intervention arm = immediate access to the brief digital imagery-competing task intervention plus symptom monitoring for 4 weeks

Delayed intervention arm = usual care for 4 weeks followed by access to the intervention plus symptom monitoring for 4 weeks

The study will enrol up to approximately 150 participants, 75 participants per study arm (see sample size calculation, section 11.1).

The study will enrol NHS ICU staff (e.g. doctors, nurses, paramedics and clinical support staff) aged 18 and over who: a) have experienced one or more work-related traumatic events during the COVID-19 pandemic (e.g. a patient death), and b) have intrusive memories of the event(s).

The study is divided into a 1-5 week screening period, randomisation into an immediate intervention or delayed intervention arm using a 1:1 overall ratio, 8 week in-study period, followed by two weeks optional qualitative interview period. Each participant will be in the study for a total of up to 17 weeks. All of the study visits will be completed by participants remotely on their smart phone or other internet enabled device.

During the in-study period participants will complete the intervention for a period of 4 weeks and will collect self-reported questionnaires at Baseline, 4 and 8 weeks digitally and remotely.

Optional qualitative interviews will be performed 4 weeks post intervention onset to assess the feasibility, acceptability and perceived value of the intervention. Information on the guidance provided by researchers to participants to explain how to use the intervention will be collected to help identify ways to train non-expert researchers to give guidance and/or digitise such guidance to establish a fully self-guided version of the intervention.

Total duration of the study from first participant enrolment to last participant completing the study is expected to last approximately 6 months.

The brief imagery-competing task intervention will be delivered on a secure web platform used for clinical self-management of health in general practice (i-spero®).

A secure web-based clinical research system, P1vital® ePRO will be used to:

- Randomise participants and will issue email/text reminders to participants and study researchers when study-related activities are due.
- Collect intrusive memory diary and intrusive memory rating data during the run-in week and at week 4 (Day 22 to 28) for all participants and at week 8 (Day 50 to 56) for participants in the delayed intervention arm.
- Collect self-reported outcome measurement data at baseline, 4 weeks (Day 28) and 8 weeks (Day 56) in both arms.

The primary comparison will be a between-groups comparison of the number of intrusive memories recorded during week 4 (i.e. from day 22 to 28; which is post intervention in arm 1 and pre-intervention in arm 2), controlling for the number of intrusive memories recorded during the run-in week. Secondary comparisons will be within-group comparisons of the number of intrusive memories in the run-in week (pre-intervention) and week 4 (Day 22 to 28) (post intervention; immediate intervention arm only) and week 4 (Day 22 to 28) (pre-intervention) and week 8 (Day 50 to 56 +7 days) (post intervention; delayed intervention arm only). After the first intervention session, both arms will have continued access to the intervention for the duration of the study period.

3.2 Study design

Participants will be recruited through the Intensive Care Society network membership and existing social media followers supplemented by targeted advertisements in social media (e.g. Facebook, Twitter).

Those who are interested in taking part in the study will be asked to complete a brief online eligibility questionnaire anonymously, which can be accessed on the study website. Participants will be asked to give online consent before completing the questionnaire. Those who meet all the inclusion criteria will be asked to provide their contact details (name, telephone number and email address). A researcher will then arrange a time to contact them by phone or video call to obtain informed consent and go through the study inclusion and exclusion criteria.
All participants will be asked to complete a daily online intrusive memory diary for a run-in period of one week where participants will be asked to record a simple count of the number of intrusive memories they have each day followed by an intrusive memory rating at the end of the week using ePRO.

Those meeting the study entry criteria will be sent a link to complete baseline questionnaires using ePRO, after completing the baseline questionnaires participants will be randomised by ePRO to receive either the immediate intervention arm or the delayed intervention arm using a 1:1 overall ratio. After

randomisation, participants will be sent information explaining what will happen next in the study. This information will differ according to whether they have been allocated to the immediate intervention or delayed intervention arm.

Participants in the immediate intervention arm will be contacted immediately by a researcher to arrange a time (e.g. via video call using Microsoft Teams) to go through the intervention for the first time (guided session: Day 1). The intervention is a 30 minute, single session task completed by the participant on their smart phone or other internet enabled device delivered on a secure web platform used for clinical self-management of health in general practice (i-spero®).

Participants in this arm will have continuous access to the intervention over the next 8 weeks and can use the intervention either on their own or with the option of researcher support. As part of the intervention, participants complete a daily record of their intrusive memories using i-spero® to identify which intrusive memories they have had, and therefore which to target with the intervention. In week 4, they will be asked to complete an intrusive memory diary during week 4 (Day 22 to 28) and intrusive memory rating at the end of week 4 (Day 28) using ePRO to assess how many intrusive memories they had each day.

Participants in the delayed intervention arm will be asked to complete the daily online intrusive memory diary during week 4 (Day 22 to 28) and intrusive memory rating at the end of week 4 (Day 28) using ePRO, to assess how many intrusive memories they had each day. The online intrusive memory diary/rating completed during week 4 will be the same as the intrusive memory diary/rating completed by all participants in the run-in week. After these first 4 weeks, they will be contacted by a researcher to arrange a video call to go through the intervention for the first time (as for the immediate intervention arm: Day 29+7 days. Participants in the delayed arm will have continuous access to the intervention over the next 4 weeks (Day 29 to 56+7 days) and can use the intervention either on their own or with the option of researcher support. As part of the intervention, participants complete a daily record of their intrusive memories using i-spero® during the 4 week period (Day 29 to 56+7 days) to identify which intrusive memories they have had, and therefore which to target with the intervention.

All participants will complete self-reported outcome questionnaires using ePRO at Baseline (prior to randomisation), 4 weeks (Day 28) and 8 weeks (Day 56).

Four to six weeks after participants started to use the intervention (and who agreed to an interview) in depth qualitative interviews with a researcher via audio or video call will be conducted.

Note: Day 1 in the immediate intervention group is defined as the day on which the participant completes the first intervention session with researcher support (guided session). The timing of this first intervention session post randomisation may vary slightly from participant to participant in the intervention arm. Day 1 for participants

in the delayed intervention arm will be paired to the timing of Day 1 for participants in the immediate intervention arm, so that the timing of the primary outcome assessment post randomisation will be approximately equal between the two groups.

This randomised optimisation study uses an adaptive Bayesian design for speed under pandemic conditions. Recent advances in trial design and methodology offer more efficient alternatives to traditional RCTs to speed up the testing and thus implementation of evidence-based treatments (ACE CONSORT Extension; Dimairo et al. 2020). Adaptive designs enable smaller, more efficient trials without loss of scientific integrity, and allow a trial to be modified on the basis of interim analysis, thereby making optimal use of data for decision-making.

Interim analyses at a group level (immediate intervention vs delayed intervention) start at e.g. n=20 and are conducted sequentially approximately between every 4-10 participants thereafter, up to a maximum of approximately n=150. Prespecified thresholds are used to trigger a potential modification of the intervention (e.g. assessed using Bayes factors which compare different hypotheses. Potential aspects of the intervention that may be tweaked for optimisation include: (i) memory reactivation procedure (e.g., to promote sufficient reactivation whilst keeping distress low); (ii) mental rotation instructions (e.g., to promote sufficient training and checking of participant understanding prior to the gameplay component); (iii) Tetris gameplay with mental rotation (e.g., to boost engagement or encourage users to self-administer the intervention more regularly).

If on the other hand we find that the intervention is working sufficiently well when delivered by the clinical psychologists on our team (Drs Lalitha Iyadurai and Veronika Kubickova), we may test the intervention with different levels of researcher-guidance; for example, delivered by a less trained individual (not a qualified clinical psychologist); and with no human guidance (non-guided). We thus include the possibility to recruit and train for intervention delivery individuals who are not clinically qualified, as we have done in previous clinical studies (e.g. Kanstrup, Singh et al. 2021). Intervention delivery by less trained individuals or without human guidance would promote scalability in the future, minimising time and resources required for rapid rollout to respond to the pandemic. Decisions around when and what to optimise in the intervention will ultimately be guided by incoming participant data and feedback; consultation with our collaborators in the Intensive Care Society Expert Advisory Panel and Data Monitoring Committee; and what is clinically sensible for the target population at the time in this pandemic.

If the intervention is shown to be significantly more effective than control (assessed using Bayes factors which compare different hypotheses) before reaching the max n=150 participants, then the optimisation study may conclude early and a follow-up pragmatic RCT, testing clinical effectiveness of the optimised intervention, can be initiated (a separate ethics application will be submitted for such a study). Precise probability thresholds will be registered prior to data analysis and after consultation with Prof Thomas Jaki on our Expert Advisory Panel. Our thinking around this has been informed by initial power estimates based on an effect size of d= 0.63 for the

primary outcome, pooled from three RCTs of this intervention Horsch et al, 2017; Iyadurai et al., 2018: Kanstrup, Singh et al. 2021). Our simulations estimate approximately 84% power to find strong evidence for the intervention by the time the maximum sample size (n=150) is reached.

4.0 Study Population

4.1 Inclusion Criteria

Potential participants will be included if they meet the following criteria:

- Aged 18 or above
- Able to read, write and speak in English
- Worked in a clinical role in an NHS Intensive Care Unit or equivalent during the COVID-19 pandemic (e.g. as a member of ICU staff or deployed to work in the ICU during the pandemic).
- Experienced at least one traumatic event related to their work during the COVID-19 pandemic, meeting criterion A of the DSM-5 criteria for PTSD: “exposure to actual or threatened death, serious injury, or sexual violence” by "directly experiencing the traumatic event(s)" or "witnessing, in person, the event(s) as it occurred to others"
- Have intrusive memories of the traumatic event(s)
- Experienced at least three intrusive memories in the week prior to screening
- Have internet access
- Willing and able to provide informed consent and complete study procedures (including briefly listing their intrusive memories (without going into any detail), and playing the computer game Tetris® with particular mental rotation instructions and completing an online intrusive memory diary).
- Willing and able to be contacted by the research team during the study period

4.2 Exclusion Criteria

Potential participants will be excluded if they meet the following criteria:

- Have fewer than three intrusive memories in the run-in week

We will not exclude those undergoing other treatment for PTSD or its symptoms, so the study is as inclusive as possible to meet the challenges ICU staff are facing during the COVID-19 pandemic.

5.0 Study Procedures

Activities taking place during the study are shown in the Time and Events table in Appendix 1.

5.1 Recruitment

Participants will be recruited through the Intensive Care Society network membership and existing social media followers supplemented by targeted advertisements in social media (e.g. Facebook, Twitter). The advertisements email

will contain a link to the study website, where potential participants will be able to read a summary of the study information including the participant information sheet and watch a video explaining what intrusive memories of traumatic events are. Study web site will also include a link to the pre-screening eligibility questionnaire.

5.2 Pre-Screening Procedures & Eligibility Assessment

Those who are potentially interested in taking part in the study will be asked to complete an online eligibility questionnaire, which can be accessed via the study website. Participants will be asked to give online consent before completing the questionnaire. The brief questionnaire is completed anonymously. Those who are not eligible to take part in the study will be sent information signposting them to NHS staff and mental health support websites, such as the NHS Every Mind Matters website. Those who meet all the inclusion criteria will be asked to provide their contact details (name, telephone number and email address). A researcher will send them a participant information sheet with full information about the study. The participant information sheet will include: the nature and purpose of the study; the study eligibility criteria; what it will involve for the participant; any risks and benefits involved in taking part; and researcher contact details in case they have any questions. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason, and with no obligation to give the reason for withdrawal. The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. If they are still interested in taking part in the study, a researcher will then arrange a time to contact them by phone or video call to obtain informed consent.

5.3 Informed Consent

Informed consent will be obtained during a phone or video call to ensure safety and adherence to the current social distancing guidelines in the pandemic. The participant and researcher will complete, sign and date the consent form using a simple electronic signature via email. Participants will be emailed a copy of the consent form. This will take place before any baseline measures or study specific procedures commence. The researcher obtaining informed consent will be GCP trained and authorised to do so by the Principal Investigator. During this meeting, the researcher will also verbally collect and record additional personal details for the participant, the NHS Trust organisation they have worked in during the COVID-19 pandemic and will go through the study inclusion and exclusion criteria with participants. These two forms will also be retained electronically in a secure format. Participants will be asked to indicate how they would prefer to be contacted during the study (e.g. by text or email).

5.4 Screening Visit Procedures (Run-in-week)

5.4.1 Intrusive memory diary

After obtaining informed consent, participants will be asked to complete a daily online intrusive memory diary for a run-in period of one week. Participants will be asked to record a simple count of the number of intrusive memories they

have each day. The intrusive memory diary is based on that used in previous studies of the brief behavioural intervention (e.g. Holmes et al., 2009; James et al., 2015; Iyadurai et al., 2018), and adapted for digital delivery using ePRO. Participants will be a sent a link to create a personal, password-protected user account to access ePRO. Each day they will receive a reminder (by text/email) to log in and complete their intrusive memory count. Intrusive memories are defined as “mental images from a traumatic event that pop suddenly into your mind when you don’t want them to” and instructions will include a link to a video explaining what intrusive memories are. Each day, the participant is asked to indicate if they have had any intrusive memories (yes/no) and if so, how many. This type of daily online intrusive memory diary has already been piloted with NHS staff with high (99.4%) completion rates (Kubickova et al., in prep). At the end of the week, they will be asked to rate how accurately they think they completed the diary over the last week (on an 11-point scale from 0 = not at all accurately to 10 = extremely accurately).

5.4.2 Intrusive memory ratings

At the end of the run-in-week, participants will be asked to rate 8 items to assess the following characteristics of their intrusive memories over the last week: frequency, distress, disruption to concentration, interference with what they were doing (how much and for how long), duration of interference, impact on work functioning (how much and how) and impact on functioning in other areas of life (how much and how). Two additional items will assess the number of days worked and number of night shifts worked in the last week.

After completing the run-in-week diary, participants will be informed by the researcher if they are eligible to continue to the next stage of the study.

5.4.3 Rescreening

The study permits the re-screening (after the end of the screening period) of participants who have consented to participate in the study but are not subsequently randomised into the study for any reason (e.g. the participant had fewer than 3 intrusive memories during the run-in week, but may have more intrusive memories at a later time). The participant will be assigned a new participant identification number, and the screening procedures must be performed again.

5.5 Randomisation and Baseline Procedures

Participants who meet the eligibility criterion of having 3 or more intrusive memories in the run-in week will be allocated to either the immediate intervention arm or the delayed intervention arm using a 1:1 overall ratio. Participants will have a 85% (rather than 50%) chance of being allocated to the arm with the fewest participants, to minimise the difference in group sizes between the two arms. This approach leads to relatively balanced groups sizes, even with small samples (Hagino et al., 2004). The randomisation program will be incorporated into ePRO to ensure that allocation cannot be influenced by the research team (i.e., randomisation is computerised and automated to ensure allocation concealment). The program will be validated by the

independent statistician. Refer to section 7.1.2 of the CSP for more information on the blinding procedures.

Before randomisation, participants will complete baseline questionnaires using ePRO. They will be asked to complete the following self-report measures:

Credibility/Expectancy Questionnaire (Devilly & Borkovec, 2000)

This 6-item questionnaire will assess participants' belief that the intervention will help reduce their intrusive memories. Wording is adapted for the current intervention: for example, the word "therapy" is changed to "intervention" and "trauma symptoms" is changed to "intrusive memories".

Demographic information

The following information is collected: age, gender identity, education level, marital status, ethnicity, employment status, number of hours per week currently working and number of years working as a healthcare professional.

Health background

A 6-item questionnaire will be used to assess current physical health problems, current treatments/medication for physical health problems, current/past mental health problems, current treatments/medication for mental health problems, family history of mental health problems and prior traumatic events.

Checklist of work-related traumatic events

Participants are asked to select from a list the types of traumatic events they have experienced or witnessed during the COVID-19 pandemic, for which they have intrusive memories. The list contains traumatic events previously reported by healthcare professionals in research literature, including a traumatic or tragic death of a patient, increased risk of COVID-19 infection, and severe or unsuccessful resuscitation.

Perceived threat to self/other

Participants are asked to rate "to what extent did you feel your life was in danger?" and "to what extent did you think that someone else's life was in danger?" on a 10-point Likert scale from 0 (not at all) to 10 (extremely). This is based on the assessment of perceived life threat used in previous prospective studies following trauma (Blanchard et al., 1995), as used in Iyadurai et al. (2018).

Peritraumatic Distress Inventory (PDI; Brunet et al., 2001)

This 13-item measure assesses the extent to which participants experienced a number of emotional reactions during the trauma. Items are rated on a 5-point Likert scale from 0 (not at all) to 4 (extremely) and a total score is calculated. The measure is internally consistent, with good test-retest reliability and good convergent and divergent validity. Peritraumatic distress was found to be one of the strongest predictors of PTSD symptoms in first responders (Marmar et al., 2006).

Impact of Event Scale-Revised (IES-R; Weiss & Marmer, 1997)

This 22-item questionnaire assesses subjective distress after a traumatic event (with reference to the events for which participants are taking part in the study). Items are rated for how distressing they have been during the past 7 days on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). Scores are calculated for the intrusion, avoidance and hyperarousal subscales and total score. The measure has good reliability and validity, and is widely used as an outcome measure in randomised controlled trials of interventions after trauma (e.g. Bryant et al., 2008).

PTSD Checklist for DSM-5 (PCL-5) 4-item version (Price et al., 2016)

This shortened 4-item version of the PCL-5 assesses symptoms of PTSD over the last month. Items are rated on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). Scores are summed to give a total severity score (ranging 0 to 16), and a cut-off score of 10 indicates a probable diagnosis of PTSD. The measure is highly correlated with the full 20-item PCL-5 and has comparable diagnostic utility.

Generalized Anxiety Disorder (GAD-2; Kroenke et al., 2007)

This 2-item short-form self-report measure assesses the severity of anxiety symptoms. Items are rated for how often they have bothered the respondent over the last two weeks, from 0 (“not at all”) to 3 (“nearly every day”). The total score ranges 0-6, with a cut-off score of 3 indicating a probable diagnosis of generalised anxiety disorder. The measure has comparable performance to the full 7-item version as a screening tool.

Patient Health Questionnaire (PHQ-2; Kroenke, Spitzer & Williams, 2003)

This 2-item short-form self-report measure assesses symptoms of depression. Items are rated for how often they have bothered the respondent over the last two weeks, from 0 (“not at all”) to 3 (“nearly every day”). The total score ranges 0-6, with a cut-off score of 3 indicating a probable diagnosis of depression. The measure has adequate construct validity with a sensitivity of 83% and a specificity of 92% for detecting major depression.

Sleep Condition Indicator (SCI; Espie et al., 2014)

This 8-item scale measures sleep problems against the DSM-5 criteria for insomnia disorder. Item responses are each scored 0-4, with scores from 0 to 2 indicating threshold criteria for insomnia disorder. Total score ranges 0-32, with a higher score indicating better sleep. The SCI is valid, reliable and sensitive to change (Espie et al, 2014; Luik et al, 2017).

Psychological Outcome Profiles Questionnaire (PSYCHLOPS; adapted by WHO, 2018)

This measure consists of 4 questions designed to assess the impact of a person’s problems. Here it will be used in relation to the impact of intrusive memories. The measure has been adapted in the World Health Organisaton (WHO) intervention package “Problem Management Plus” from Version 5 of the Psychological Outcome Profiles Questionnaire (PSYCHLOPS). The adapted version used in the WHO publication (a) does not ask when the person became concerned about the problem; (b) asks how people have felt this last week rather than how they have felt in

themselves this last week (Q4); (c) probes for a problem description; and (d) uses the word “intervention” rather than “therapy”.

World Health Organization Disability Assessment Schedule (WHODAS) 2.0

The 12-item, self-report version of the WHODAS 2.0 will be used to assess difficulties in relation to the impact of intrusive memories. Respondents rate how much difficulty they have had in each area in the past 30 days, from 0 (none) to 4 (extreme or cannot do). The measure showed high internal consistency (Cronbach alpha=.83-.92), high 2-week test-retest reliability (intraclass correlation coefficient=.83), adequate construct validity, and was sensitive to change when administered online to individuals with anxiety and stress disorders (Axelsson et al., 2017).

EQ-5D-5L (Herdman et al., 2011)

The 5-level version of the EuroQol-5D (EQ-5D-5L) is a brief measure for assessing general quality of life and health status. Items assess mobility, self-care, usual activities, pain/discomfort and anxiety/depression each on a 5-point scale. Respondents rate their overall health today from 0 (the worst health you can imagine) to 100 (the best health you can imagine).

Sickness absence (Revicki et al., 1994)

A single item will assess the number of sick days taken from work during the past 4 weeks.

Scale of work engagement and burnout (SWEBO; Hultell & Gustavsson, 2010)

This 18-item self-report measure assesses work engagement and burnout. The work engagement subscale consists of 9 items assessing three dimensions (vigour, attentiveness, dedication). The burnout subscale also consists of 9 items assessing with three dimensions (exhaustion, disengagement and inattentiveness). Respondents rate how often they have felt each descriptive in the past two weeks, from 1 (not at all) to 4 (all the time). The mean score is calculated for each subscale.

Support from managers and from family/friends

A 2 item questionnaire asks “During the COVID-19 pandemic, how well supported have you been by your supervisors/managers?” The response is rated as “not at all”, “quite a bit”, “moderately”, “quite a bit”, or “extremely” (Greenberg, 2021, personal communication). The second questionnaire items asks “how well supported have you been by your family/friends?” rated using the same response format.

Intention to leave job (Cohen, 1998)

3 items are used to assess participants’ intention to leave their job e.g. “I think a lot about leaving the job”, each rated from 1 (strongly agree) to 5 (strongly disagree). The total score ranges 3 to 15, with a lower score indicating stronger intention to leave the job.

Changes to health and work

At week 4 and 8 participants in both arms complete a 6-item questionnaire. This questionnaire will be used to assess the occurrence of any new traumatic events, any additional stressful life events (e.g. relationship problems, financial problems), new treatments received, social support received, changes to the job, or changes to the number of hours worked per week since the last assessment.

Note: Changes to health and work questionnaire is not required to be completed at baseline.

5.6 Intervention procedures

After completing baseline questionnaires, participants will be sent information explaining what will happen next in the study. This information will differ according to whether they have been allocated to the immediate intervention or delayed intervention arm. Participants in the immediate intervention arm will be contacted to arrange a time to go through the digital intervention instructions with them for the first time (see below). They will then have access to the digital intervention for 4 weeks. Participants in the delayed intervention arm will be asked to complete the online intrusive memory diary and intrusive memory ratings using ePRO (as for the run-in week, section 5.4), at week 4. They will then be contacted by a researcher to arrange a time to go through the digital intervention instructions with them (as in the immediate intervention group). They will have access to the digital intervention for the next 4 weeks.

5.6.1 Digital intervention

The brief, digital intervention is a 30-minute, single-session task completed by the participant on their smart phone or other internet-enabled device. It includes animated videos to explain what the intervention is and how to do it, and takes participants through each step one at a time. The intervention will be delivered on a secure web platform used for clinical self-management of health in general practice (i-spero®). Participants will be a sent a unique registration code to create a personal, password-protected user account to access the intervention.

Participants will be contacted by the researcher to arrange a video call to run through the intervention with them for the first time. The investigator team may audio-record the guided intervention sessions using Microsoft Teams for training and treatment fidelity assessment purposes. For those in the immediate intervention arm, this will be as soon as possible after completing baseline questionnaires. For those in the delayed intervention arm, this will be approximately 4 weeks after completing baseline questionnaires. During this session, the participant will be asked to briefly list the different intrusive memories they have and choose the one they wish to target first (“list of intrusive memories (hotspots)” – see below). They will then be asked to complete the intervention, which includes several key components: a) the participant is asked to briefly bring to mind the intrusive image as a reminder to the specific memory, b) they receive instruction on how to play the computer game Tetris using “mental rotation”, and c) they are asked to play Tetris using mental rotation for at least 20 minutes. During the intervention, participants

are asked to rate how distressed they are feeling on 3 occasions (“distress rating” – see below), to rate the vividness of the image that is brought to mind ("reactivation vividness rating” – see below), and to rate how much they were able to follow mental rotation instructions (“mental rotation rating” – see below), to assess adherence to the instructions. After this first session, participants may use the intervention as many times as they like over the next 4 weeks (e.g. to target other intrusive memories or those that recur), either on their own or with the option of researcher support. Intervention use and compliance will be assessed and monitored.

Within-intervention measures:

List of intrusive memories (hotspots)

Participants are asked to briefly list the content of the different intrusive memories they are having i.e. a few words to describe the image that pops up for each e.g. “seeing the patient’s face”. They are asked to move quickly from one to the next, and not to think about their memories in any detail.

Distress rating

Participants are asked to rate how distressed they are feeling right now, on a 11-point rating scale from 0 = not at all distressed to 10 = extremely distressed. This measure is given before the memory reminder cue, after the memory reminder cue, and after playing Tetris.

Reactivation vividness rating

After the memory reminder cue, participants are asked to rate how vividly they saw the intrusive memory in their mind, rated as 1 = no image at all, 2 = vague and dim, 3 = moderately clear and vivid, 4 = clear and reasonably vivid and 5 = perfectly clear and as vivid as normal vision.

Mental rotation rating

After playing Tetris, participants are asked to rate how closely they were able to follow instructions i.e. plan ahead and visualise where to play the blocks coming up next, on a 11-point rating scale from 0 = not at all closely to 10 = extremely closely.

Record of intrusive memories

During the 4-week period participants have access to the intervention, they will be asked to complete a daily record of their intrusive memories using the same web platform as the intervention (i-spero®), to identify which intrusive memories they have had (in addition to how many). The purpose of recording intrusive memories in this way is to identify when participants might benefit from repeating the intervention, i.e. when they have intrusive memories. If they record the occurrence of intrusive memories, they will be given the option of repeating the intervention to target those intrusive memories.

5.6.2 Intervention accessibility post trial end date

The digital intervention will be made available to all participants who have requested to keep having continued access to the intervention after the trial's end date (please refer to section 5.8 of the protocol for more information on end of trial definition). Those participants who have requested to keep their access will have continued access to non-guided version of the intervention for a period of 12 months after they have completed the trial.

5.7 In study procedures

5.7.1 Week 1 (D1 to D7)

Immediate Intervention Arm:

- On Day 1 the participant meets with the researcher (virtual visit) to complete the intervention for the first time. Each time the participant completes the intervention they will choose an intrusive memory to work on, complete distress ratings (x3), play Tetris® using mental rotation, complete a reactivation vividness rating and a mental rotation rating (for further detail of the intervention see section 5.6.1 Digital intervention). Following the completion of the first intervention, participants in this arm will have continued access to the intervention for 4 more weeks (D28).

All participants in the immediate intervention arm will use i-spero® to complete a daily record of intrusive memories for 4 weeks and access the intervention.
Delayed Intervention Arm:

- During week 1 participants in the delayed intervention arm are not required to complete any procedures.

5.7.2 Week 2&3 (D8 to D21)

Immediate Intervention Arm:

- During week 2 and 3 participants in the immediate intervention arm will have continuous access to the intervention on i-spero®.

Delayed Intervention Arm:

- During week 2 and 3 participants in the delayed intervention arm are not required to complete any procedures.

5.7.3 Week 4 (D22 to D28)

Immediate Intervention Arm:

- All participants in the immediate intervention arm will be asked to complete the online questionnaires at the end of week 4 (D28), including IES-R, PCL-5 4-item version, GAD-2, PHQ-2, SCI, PSYCHLOPS, WHODAS, EQ-5D-5L, Number of sick days, Scale of Work Engagement and Burnout (SWEBO), Intention to leave job, in addition to changes to health and work on ePRO.

- All participants in the immediate intervention arm will have continuous access to the intervention and at the end of week 4 (D28) will be asked to complete the daily intrusive memory diary during week 4 (D22 to D28) on a daily basis followed by intrusive memory ratings at the end of week 4 (D28) on ePRO.

Delayed Intervention Arm:

- All participants in the delayed intervention arm will be asked to complete the daily intrusive memory diary during week 4 (D22 to D28) on a daily basis followed by intrusive memory rating at the end of week 4 (D28) on ePRO.
- All participants in the delayed intervention arm will be asked to complete the online questionnaires at the end of week 4 (D28) including IES-R, PCL-5 4-item version, GAD-2, PHQ-2, SCI, PSYCHLOPS, WHODAS, EQ-5D-5L, Number of sick days, Scale of Work Engagement and Burnout (SWEBO), Intention to leave job, in addition to changes to health and work on ePRO.

5.7.4 Week 5,6 & 7 (D29 to D49)

Immediate Intervention Arm:

- All participants in the immediate intervention arm are not required to complete any procedures during week 5, 6 and 7, but continue to have access to the intervention on i-spero® (for optional use).

Delayed Intervention Arm:

- On Day 1 of Week 5 (D29+7 days), the participant meets with the researcher (virtual visit) to complete the intervention for the first time. Each time the participant completes the intervention they will choose an intrusive memory to work on, complete distress ratings (x3), play Tetris® using mental rotation, complete a reactivation vividness rating and a mental rotation rating (for further detail of the intervention see section 5.6.1 Digital intervention). Following the completion of the first intervention, participants in this arm will have continued access to the intervention for 4 more weeks (D56+7 days).All participants in the delayed intervention arm will use i-spero® to complete a daily record of intrusive memories for 4 weeks (from Week 5 to 8+7 days inclusive) and access the intervention.

5.7.5 Week 8 (D50 to D56)

Immediate Intervention Arm:

- All participants in the immediate intervention arm will be asked to complete the intrusive memory rating at the end of week 8 (D56).
- All participants in the immediate intervention arm will be asked to complete the online questionnaires at the end of week 8 (D56), including IES-R, PCL-5 4-item version, GAD-2, PHQ-2, SCI, PSYCHLOPS, WHODAS, EQ-5D-5L, Number of sick days, Scale of

Work Engagement and Burnout (SWEBO), Intention to leave job in addition to changes to health and work on ePRO.

Delayed Intervention Arm:

- All participants in the delayed intervention arm will be asked to complete the online questionnaires at the end of week 8 (D56+7 days), including IES-R, PCL-5 4-item version, GAD-2, PHQ-2, SCI, PSYCHLOPS, WHODAS, EQ-5D-5L, Number of sick days, Scale of Work Engagement and Burnout (SWEBO), Intention to leave job, in addition to changes to health and work on ePRO.
- All participants in the delayed intervention arm will have continuous access to the intervention and the record of intrusive memories at the end of week 8 (D56+7 days) will be asked to complete the daily intrusive memory diary during week 8 (D50 to D56) on a daily basis followed by intrusive memory ratings at the end of week 8 (D56) on ePRO.

5.7.6 Intervention feedback

After the 4-week intervention period, participants in both arms will be asked to complete an online feedback questionnaire about their experience of using the intervention, as well as an optional qualitative interview.

5.7.7 Feedback questionnaire

A 12-item questionnaire will assess participants' experience of using the intervention. The first ten items assess how easy, helpful, distressing, burdensome and acceptable participants found the intervention, how willing they would be to use it in the future, how confident they would be in recommending it to a friend and how much they feel it could be used to support staff within NHS ICUs, each rated from 0 (not at all) to 10 (very). The last two items ask how the intervention could be improved, for any other comments or suggestions about the intervention, and for the occurrence of any adverse events, all with an open response.

5.7.8 Optional qualitative interview

Participants will be given the option of completing a qualitative interview with a researcher via audio or video call. This semi-structured interview will consist of a number of questions designed to gain an in-depth understanding of participants' experience of using the intervention and, including acceptability, improvement suggestions, training/psychoeducation materials, potential barriers/facilitators to recruitment and uptake, and support needed for remote intervention delivery. The interview will be audio-recorded (using a password-protected digital voice recorder) and will last approximately 30 minutes.

5.8 Definition of End of Trial

The end of the study is defined as the date that the last participant completes their final online assessment (8 weeks post intervention in the immediate intervention

arm / equivalent timeframe in the delayed intervention arm) and final qualitative interview has been completed.

As described above (section 3.2 Study design), a strength of this adaptive Bayesian design is that interim analyses can guide decision-making, such as when to adjust aspects of the intervention to optimise its effect, and when sufficient evidence has been collected to end this optimisation trial and proceed to follow-up confirmatory testing. In the event that the probability that the intervention is more effective than control exceeds e.g. 90% at any point (i.e., before reaching the max n=150), this optimisation study may conclude early and a follow-up pragmatic RCT, testing clinical effectiveness of the optimised intervention, can be initiated (a separate ethics application will be submitted for such a study). Precise probability thresholds will be registered prior to data analysis and after consultation with statisticians Dr David Moreau and Prof Thomas Jaki on our Expert Advisory Panel.

5.8.1 Debrief

Following the end of the final outcome assessment (8 weeks post intervention), participants will be sent information by email about the overall study design, how they can access further information about the study once published, and where they can access further mental health information online if needed. They will be given details on how they can contact the research team if they have any questions, concerns or comments about the study.

5.9 Completion and Discontinuation / Withdrawal

A participant will be considered to have completed the study if they have completed all study procedures up to and including the assessments.

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- An adverse event that results in participant no longer being able to comply with study procedures.
- Significant protocol deviation
- Withdrawal of consent

In all cases, the reason for withdrawal will be recorded.

5.10 Study Termination

The Sponsor reserves the right to terminate the study at any time. Reasons for the early termination of a study by the Sponsor, may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the Sponsor's procedures, or GCP guidelines;
- Safety concerns;

- Inadequate recruitment of participants.

We note that if the Investigators choose to end the study before reaching the maximum sample size of approximately n=150, based on strong evidence for an effect of the intervention, this would not be considered as "Study Termination" but would reflect a potential outcome of this optimisation study design.

6.0 Trial Intervention

6.1 Description

This brief imagery-competing task intervention consists of a brief reminder cue to the specific intrusive memory, followed by playing the computer game Tetris for 20 minutes with instructions to use mental rotation during game play. The study team will provide a single training session on completing the intervention for the first time (guided session). The intervention can then be repeated for other intrusive memories.

Refer to section 5.6.1 for more information about the digital intervention.

The brief digital intervention will be delivered using a secure web platform used for clinical self-management of health in general practice (i-spero®).

The intervention is not a medical device as it does not have a medical purpose.

6.2 Instructions for Use

Instructions for use are included within the intervention itself, both digitally (e.g. via videos) and through researcher guidance (virtual visit). Participants will receive instructions on how to identify and list their intrusive memories, how to select and reactivate an intrusive memory, and how to play the computer game Tetris using "mental rotation". They are asked to play Tetris using mental rotation for at least 20 minutes.

6.3 Manufacturer and Distributor Details

The brief digital intervention on i-spero® is owned and manufactured by P1vital Products Ltd. Tetris® has been licenced for use within i-spero® from The Tetris Company.

6.4 Computer System Validation

ePRO, i-spero® and the brief digital intervention have been developed following a formal computerised system validation methodology which complies with GCP, FDA 21CFR Part 11 and ISO13485 Quality Management System.

6.5 Support and Assistance

In the event that difficulties are experienced with ePRO or i-spero®, researcher or participants should notify P1vital Products Ltd. (telephone number +44 (0)1865522088; email itsupport@p1vital.com). Any Adverse Device Effects or device deficiencies must be reported in accordance with Section 10.2.

7.0 Randomisation

7.1.1 Procedure to be followed

Participants who meet the entry criteria during the screening visit and after the run in week will be randomised into one of two study arms.

After randomisation, the study researcher will not tell the participant which study arm they are assigned.

The study researcher will contact the participant at the appropriate time based on which arm they have been allocated to schedule a virtual meeting to support the participant completing the brief digital intervention for the first time.

The study researcher will provide information for the participant to set up a user account on i-spero® to access the intervention.

After the first time the intervention has been completed participants will have the option of being contacted by a researcher to complete the intervention again and/or complete the intervention on their own.

7.1.2 Blinding of Study Intervention

Statisticians will be blinded to allocation, and all assessments are self-report questionnaires administered digitally, eliminating assessor bias (i.e., to ensure blinding of outcome assessment). As all eligible participants are randomised to receive the intervention, but at two different time points, all will be told that they will receive the intervention and have access to it for 4 weeks at some point over the next 8 weeks. They will also all be informed that they will be asked to complete an online daily intrusive memory diary for some of those weeks. Researchers involved in contacting the participants and facilitating the conduct of intervention will not be blinded: however, as both arms receive the same intervention but at different time points (and the same clinicians will be administering the intervention in both arms), clinician motivation is likely to be unbiased (thereby minimising performance bias on part of the clinician). The remaining principal investigator's delegated study members will also be unblinded during the length of the trial.

8.0 Adverse Event Reporting

8.1 Definitions

8.1.1 Adverse Event (or adverse experience) (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in subjects, users or other persons, whether or not related to the brief digital intervention.

NOTE 1: This definition includes events related to the procedures involved.

8.1.2 Serious Adverse Event (SAE)

Any adverse event, respectively, that:

- results in death.
- is life-threatening.

Note: the term “life-threatening” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe;

- requires hospitalisation or prolongation of existing hospitalisation.

  Note: any event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of these outcomes;

- results in persistent or significant disability or incapacity

  Note: any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and / or quality of life;

- consists of a congenital anomaly or birth defect

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

8.2 Safety Reporting Procedures

No major risks are expected in association with any part of the study methodology or intervention. The brief behavioural intervention is non-invasive, minimally distressing, and no study-related adverse events have been reported in any previous trials or studies testing the intervention. In this trial, any adverse events will be self-reported at 4-week and 8-week assessment. In the event that any adverse events are reported by participants, this will be reviewed by the Chief Investigator in the first instance, and with a clinical colleague in the research team as necessary. If a serious adverse event is identified (i.e. meeting the definition in section 8.1.2 above), this will be reported to the REC (in line with section 8.2.2 below).

As in any study, and unrelated to the study methodology, there may be participants for whom significant risk to themselves or others becomes apparent during the study period, e.g. through spontaneously reporting suicidal intent during contact with the research team or in open-response questionnaire items. In these cases, the research team will encourage the participant to seek help e.g. contact their GP or other relevant healthcare provider. Any such instances will be discussed within the research team and recorded appropriately.

At the end of the study, all participants will be sent information about access to mental health support, such as the NHS/Every Mind Matters website, the Intensive Care Society Wellbeing Hub webpage and advice to contact their GP/occupational health team.

Additionally, if at any point during the study the participant reveals information that may suggest professional malpractice, they will be encouraged by the researcher to report this to their Hospital's Freedom To Speak Up (FTSU) Guardian and/or to follow their Trust Whistleblowing Policy.

8.2.1 All Adverse Events

All adverse events will be reported from the time a signed and dated informed consent form is obtained until completion of the last study-related procedure.

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention (if applicable), must be recorded on the paper AE forms designed for this study.

8.2.2 Serious Adverse Events

Research staff must record SAEs that meets the criteria described in section 8.2 on the serious adverse event form and report that to the Chief Investigator immediately (maximum within 24 hours of their knowledge of the event). The initial report of an SAE may be made by telephone and this must be followed up by written confirmation (for example by facsimile (fax) or e-mail).

The Chief Investigator will report SAEs immediately to the study Sponsor (maximum within 24 hours of research staff knowledge of the event).

SAE and Incident reporting numbers:

Telephone: 44(0)1865 522 030

Facsimile: +44(0)1865 597 673

Email: admin@p1vital.com

The initial report may be made by telephone and this must be followed up by written confirmation.

Note: P1vital Products Ltd and the Chief Investigator have the same contact details. Safety information will be circulated internally within 24 hours of receipt.

8.2.3 Reporting to Research Ethics Committees and other bodies

An SAE occurring to a research participant should be reported to the main Research Ethics Committee where, in the opinion of the Chief Investigator, the event was:

- Related – that is, it resulted from administration of any of the research procedures or intervention.
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

The Chief Investigator will report all related, unexpected SAEs to the Research Ethics Committee within 15 days of their becoming aware of the event. The report must be made using the appropriate national/international SAE report forms (e.g. SAE report form for non-Clinical Trials of Medicinal

Products, available from the Health Research Authority (HRA) website in the UK).

9.0 Primary and Secondary Endpoints

9.1 Primary Endpoint

- Number of intrusive memories of traumatic events recorded by participants in a brief daily online intrusive memory diary for 7 days during week 4 (i.e. from Day 22 to 28 post first intervention session in immediate intervention arm/equivalent timeframe in delayed intervention arm). Analysed as between-group comparison (immediate intervention arm vs. the delayed intervention arm) controlling for the number of intrusive memories during the run-in week.

9.2 Secondary Endpoint

- Number of intrusive memories recorded by participants in a brief daily online intrusive memory diary for 7 days during the run-in week (pre-intervention) and week 4 (Day 22 to 28) in the immediate intervention arm; and during week 4 (Day 22 to 28) and week 8 (Day 50-56+7 days) in the delayed intervention arm (i.e. within-group comparisons).
- Intrusive memory ratings (distress, disruption to concentration/functioning: how much and how), Impact of Event Scale-Revised (IES-R), PTSD Checklist for DSM-5 (PCL-5) 4-item, Generalised Anxiety Disorder-2-item questionnaire (GAD-2), Patient Health Questionnaire-2-item version (PHQ-2), Sleep Condition Indicator (SCI-08), Physiological Outcome Profile Questionnaire (PSYCHLOPS), World Health Organization Disability Assessment Schedule (WHODAS), 5-level EQ-5D (EQ-5D-5L), Number of sick days, Scale of Work Engagement and Burnout (SWEBO), Intention to leave job at week 4 (i.e. Day 28 post first intervention session in immediate intervention arm/equivalent timeframe in delayed intervention arm) in the immediate intervention arm vs. the delayed intervention arm (i.e. between-groups comparison).
- Intrusive memory ratings (distress, disruption to concentration/functioning: how much and how), Impact of Event Scale-Revised (IES-R), PTSD Checklist for DSM-5 (PCL-5) 4-item, Generalised Anxiety Disorder-2-item questionnaire (GAD-2), Patient Health Questionnaire-2-item version (PHQ-2), Sleep Condition Indicator (SCI-08), Physiological Outcome Profile Questionnaire (PSYCHLOPS), World Health Organization Disability Assessment Schedule (WHODAS), 5-level EQ-5D (EQ-5D-5L), Number of sick days, Scale of Work Engagement and Burnout (SWEBO), Intention to leave job at baseline, 4 weeks (Day 28) and 8 weeks (Day 56) in the immediate intervention arm; and at 4 weeks (Day 28) and 8 weeks (Day 56+7 days) in the delayed intervention arm (i.e. within-group comparisons).

9.3 Tertiary Endpoint

- 8-item questionnaire (changes to health and work) at4 weeks (Day 28) and 8 weeks (Day 56) (both arms).

- Rates of recruitment, intervention use/adherence, outcome measure completion and participant attrition. (examples of adherence include how long they played Tetris for; mental rotation compliance rating; and if the participant experienced an intrusive memory in the diary, whether they then engaged in the intervention and focussed it on that memory specifically rather than a different memory)

- Feedback questionnaire at 4 weeks post first intervention session in both arms (i.e. Day 28 in the immediate intervention arm and Day 56 in the delayed intervention arm).
- Optional qualitative interview at 4 to 6 weeks post first intervention session in both arms (i.e. Day 29+14 days in the immediate intervention arm and Day 57+14 days in the delayed intervention arm).
- Optional qualitative interview information about guidance given by the expert/non expert researchers to help participants to learn how to use the intervention.

10.0 Data Handling

10.1 Source Data Collection

Source documents are original documents, data and records. These include, but are not limited to, study related documents e.g. Informed consent form, ePRO questionnaire data, i-spero® intervention data, Adverse events.

The following data will be recorded in the study file (paper source):

- Participant information sheet
- Eligibility Questionnaire
- Consent form
- Contact details
- Inclusion/Exclusion Criteria
- Intrusive memory daily and weekly data (missed during electronic source entry)

The following data will be recorded directly into the ePRO system by participant (electronic source):

- Intrusive memory diary (daily)
- Intrusive memory rating (end of week)
- Randomisation
- Credibility/Expectancy Questionnaire
- Demographics
- Health background
- Checklist of traumatic events
- Perceived threat to self/other
- Peritraumatic Distress Inventory
- Support from managers and from family/friends
- Impact of Event scale-Revised (IES-R)
- PTSD Checklist for DSM-5 (PCL-5)
- Generalised Anxiety Disorder (GAD-2)

- Patient Health Questionnaire (PHQ-2)
- Sleep Condition Indicator
- Psychological Outcome Profiles Questionnaire (PSYCHLOPS)
- World Health Organisation Disability Assessment Schedule (WHODAS) 2.0
- EQ-5D-5L (5-LEVEL EuroQol 5D)
- Sickness absence
- Scale of Work Engagement and Burnout (SWEBO)
- Intention To Leave Job
- Changes to health and work

The following intervention data will be recorded directly into the i-spero® system (electronic source).

- Intervention: List of intrusive memories (hotspots)
- Intervention: Distress rating (x3)
- Intervention: Reactivation vividness rating
- Intervention: Mental rotation rating
- Intervention: Record of intrusive memories (daily)
- Feedback Questionnaire

The following data will be recorded directly on audio files and stored in the study file (electronic source).

- Qualitative interviews

10.2 Data Entry / Management

Questionnaire and intervention task data will be collected and stored electronically in the P1vital® ePRO and i-spero® systems. These two systems will be set up, hosted and managed by P1vital Products Ltd, and have been developed, validated and qualified in accordance with regulatory requirements for computerised systems used in clinical research/practice (see further details below). Data will be collected using a unique study-specific ID code for each participant, and the only personal identifiable data collected using these systems will be the participant's first name, email address and mobile phone number, to send them automated emails/texts and reminders about the study procedures. Data will be stored securely on their server until deletion is requested by the research group after the study has terminated and all relevant data has been transferred to the research team. Personal identifiable data will be deleted automatically once a participant completes the study, of if they are not eligible after completing the baseline count of their intrusive memories.

Anonymised datasets, sent in encrypted files in a .csv/.xlsx file format, will be securely transferred to the research team for statistical analysis. Participants will be identified by an ID code in any database, and their name and any other identifying details will NOT be included in any study data electronic file. During screening, potential participants are asked to complete an anonymous eligibility questionnaire on the study website. Eligible participants will be asked to provide their name, telephone number and/or email address. These data will be deleted as soon as they

are no longer needed to contact the participant. Anonymous consent data will be downloaded from the study website. Electronic data will be stored on a secure file server which is firewall and password protected. Study data (including consent forms) will be kept for at least 3 years after final publication/public release, and de-identified data may be archived in an online repository.

Documents containing personal information (e.g. consent form and participant contact details) and audio-recordings will be stored separately from other study data, in password-protected files on secure file servers, and only accessible by study staff and authorised personnel. (Note, personal data will not be stored on paper documents due to remote working during the COVID-19 pandemic). Personal data (apart from consent forms) will be kept for a maximum of 6 months after the end of the study, after which time it will be destroyed (files will be deleted). If participants give consent to be contacted about future research, their contact details will be held in a password-protected database, until they are no longer required.

10.3 P1vital Products Data Security Policies and Procedures

P1vital Products Ltd is fully compliant with the UK Data Protection Act 2018 and has appropriate data security policies and procedures in place. The P1vital® ePRO and i-spero® systems are hosted by Amazon Web Services, EU West 1 region (Ireland). The P1vital® ePRO and i-spero® systems administration and support is provided by a third party, Elysium Ltd, who are ISO27001 and ISO9001 certified. P1vital Products Ltd and Elysium Ltd are registered with the Information Commissioners Office, who are responsible for the enforcement of UK data protection.

The P1vital® ePRO and i-spero® systems are only accessible through a secure encrypted web address (https//: web access), via a unique user ID and secure password. All non-study participant users must complete a security access request form to be registered and authorised to use the system. All personal identifiable data is stored in an encrypted form in the application database. The encryption key is only known by 3 system administrators (one primary and two backup personnel) at Elysium Ltd who support the P1vital® ePRO and i-spero® systems. No employees of P1vital Products can access the database or the encryption key.

11.0 Statistical Methods and Data Analysis

This randomised optimisation study uses an adaptive Bayesian design for speed under pandemic conditions. Recent advances in trial design and methodology offer more efficient alternatives to traditional RCTs to speed up the testing and thus implementation of evidence-based treatments (ACE CONSORT Extension; Dimairo et al. 2020). Adaptive designs enable smaller, more efficient trials without loss of scientific integrity, and allow a trial to be modified on the basis of interim analysis, thereby making optimal use of all data for decision-making.

A brief statistical analysis plan (optimisation SAP) will be prepared prior to the first interim analysis, based on the primary outcome (number of intrusive memories at week 4) that will guide trial adaptation and optimisation.

A second statistical analysis plan for independent analysis of the complete trial data will be prepared prior to database lock (standard SAP - end of Study Analysis. Using standard statistical methods). Below is an outline of the sample size calculations and the main statistical analyses to be performed on the complete trial data.

11.1 Sample Size

Interim analyses at a group level (immediate intervention vs delayed intervention) start with a small number of participants (e.g. n=20) and are conducted sequentially every approximately between 4-10 participants thereafter, up to a maximum of approximately n=150. Prespecified thresholds are used to trigger a potential modification of the intervention (e.g. assessed using Bayes factors which compare different hypotheses. If the intervention is shown to be significantly more effective than control (assessed using Bayes factors which compare different hypotheses) before reaching the max n=150 participants, then the optimisation study may conclude early and a follow-up pragmatic RCT, testing clinical effectiveness of the optimised intervention, can be initiated (a separate ethics application will be submitted for such a study). Our thinking around this has been informed by initial power estimates based on an effect size of d= 0.63 for the primary outcome, pooled from three RCTs of this intervention Horsch et al, 2017; Iyadurai et al., 2018: Kanstrup, Singh et al. 2021). Our simulations estimate 84% power to find strong evidence for the intervention by the time the maximum sample size (n=150) is reached.

11.2 Data Set for Analysis

All analyses will be conducted on an intention to treat (ITT) basis. The ITT is defined as all randomised participants.

11.3 Description of Statistical Methods

Prof Emily A Holmes, and Dr Lalitha Iyadurai will work with collaborators and statisticians (Prof Mike Bonsall and Varsha Ramineni, Prof Thomas Jaki and Dr Boliang Guo to develop the statistical analysis plan and to analyse the data. A pre-specified analysis script will be preregistered prior to data analysis (e.g., on the Open Science Framework).

11.3.1 Study Design Analysis

Ongoing sequential analysis using Bayesian statistical approaches will be used to evaluate the study design based on the primary outcome (difference in the number of intrusive memories in week 4 for groups of participants. The analysis will control for the number of intrusive memories during the run in week. Exploratory data analysis will be used to investigate the distribution of the primary outcome measure. Patterns of missing data will be explored and will be imputed as necessary. In the case where we see excess zeros (i.e., zero inflation) we will explore treating this with the use of an alternative statistical model (e.g., zero inflated Poisson GLM, negative binominal). This is further explained in the statistical analysis plan for designing the study.

11.3.2 End of study Analysis

Standard statistical methods will be used to analyse the complete trial data. The sections below (11.3.3 – 11.3.5) give a brief overview of these planned analyses.

Outcome measures will be tested for assumptions of the planned analyses, and where assumptions are violated (e.g., normality of residuals), data will be either transformed or analysed using a non-parametric test.

Sensitivity analyses will be conducted to examine whether analytical decisions (e.g., the exclusion of outliers or inclusion of covariates in analyses) influences the results.

For tertiary analyses (section 11.3.3 below), a combination of descriptive and qualitative analyses will be used. This end of study analysis will be conducted by the University of Nottingham.

11.3.3 Analysis of Primary Objective:

A between-groups analysis will be used to test the difference in the number of intrusive memories in week 4 (i.e. from Day 22 to 28) between the immediate intervention and delayed intervention groups. The analysis will control for the number of intrusive memories during the run-in week.

11.3.4 Analysis of Secondary Objectives:

As all measures will be repeatedly measured, multilevel modelling will be used to examine the group comparison at 4th week and derive the change estimate from baseline to each follow-up time, with patient as level two analytical unit, baseline measure, treatment arm, following up time and the interaction of arm × time as covariate.

A within-group analysis will be used to test the change in the number of intrusive memories from the run-in week to week 4 (Day 22 to 28) in the immediate intervention group.

A within-group analysis will be used to test the change in the number of intrusive memories from week 4(Day 22 to 28) to week 8 (Day 50 to 56+7 days) in the delayed intervention group.

Between-groups analyses will be used to test for differences in other secondary outcomes at 4 weeks between the immediate intervention and delayed intervention groups: intrusive memory ratings of distress and disruption to concentration / functioning; symptoms of post-traumatic stress, anxiety, depression and insomnia; sickness absence; work engagement and burnout; intention to leave job; functioning and quality of life.

Within-group analyses will be used to test the change in other secondary outcomes (listed above) from baseline to 4 weeks in the immediate intervention group.

Within-group analyses will be used to test the difference in other secondary outcomes (listed above) from 4 weeks and 8 weeks in the delayed intervention group.

Within-group analyses will be used to test if changes in secondary outcome measures are maintained at 8 weeks post intervention onset in the immediate intervention arm.

11.3.5 Analysis of Tertiary Objectives

Acceptability questionnaires will be reported using descriptive statistics. Free text comments will be analysed thematically. Questionnaire and demographic data will be used to guide sampling for the semi-structured interviews.

Interview data will initially be thematically analysed using an inductive thematic, constant comparison approach based on grounded theory (Glaser and Strauss 1967). Once a thematic analysis has been carried out and key themes identified, data will be explored for suitability in relation to normalisation process theory (or an alternative framework drawn from implementation science, addressing key aspects such as the intervention's design and fit within clinical practice, if more suitable). This will be complemented by the questionnaire data, which will provide quantitative data that includes aspects of normalisation process theory. Normalisation process theory is a sociological theory developed and tested to understand the implementation of new ways of working (including technology) in health care, including depression and in primary care (May et al. 2009). It is likely that we will use normalisation process theory to explore implementation of the intervention. However, using a predetermined analytical framework precludes a more inductive approach and risks the exclusion of relevant insight that is not discernible through that particular analytical lens. For this reason, choice of analytical framework will be informed by its appropriateness to the data (MacFarlane and O'Reilly de Brun 2012).

Both the questionnaire and interview data will be used to develop an inductive analysis of the value and implementation of the intervention. This type of inductive analysis will further our understanding of how the intervention is used and if changes could be made to enhance its implementation and facilitate its adoption.

Descriptive statistics will be used to summarise data regarding support from managers and family/friends and changes to health and work in the two groups.

Descriptive statistics will be used to summarise rates of recruitment, intervention use/adherence, outcome measure completion and

participant attrition.

Descriptive statistics will be used to summarise quantitative data regarding intervention acceptability (feedback questionnaire)

Qualitative interview data will be thematically analysed using an inductive thematic, constant comparison approach based on grounded theory (Glaser and Strauss 1967).

12.0 Quality Control and Quality Assurance

Regular monitoring will be performed to verify that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The Investigator will allow the monitor to carry out study monitoring at regular intervals, depending on the recruitment rate, and at times arranged by mutual agreement.

Quality assurance representatives from the Sponsor or P1vital may visit to carry out an audit of the study in compliance with regulatory guidelines and relevant standard operating procedures.

The Investigator will allow monitors and other persons responsible for audits to:

- meet all members of his / her team involved in the study,
- consult all of the documents relevant to the study,
- directly access source documents to check,
- verify that the study is carried out in compliance with the protocol and local regulatory requirements.

All information dealt with during these visits will be treated as strictly confidential.

13.0 Data Monitoring Committee

An independent data monitoring committee including a psychologist, clinician, statistician and other appropriate members from the expert advisory panel will be appointed. The Data Monitoring Committee will review trial data and will advise the Sponsor whether changes to the protocol are advisable in light of safety, optimisation, recruitment and retention of participants and/or sample size.

Any changes to optimise the intervention procedures will be decided by members of the Data Monitoring Committee.

14.0 Regulatory and Ethical Obligations

14.1 Regulatory Framework

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996 – the author should confirm which version is preferred by the sponsor at the time of writing), the principles of GCP and in accordance with all applicable

national and international regulatory requirements, including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, and any subsequent amendments.

14.2 Approvals

The study protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC) for written approval. Any subsequent updates to these documents will also be sent to the REC for their approval prior to use in the study.

14.3 Study Reports

Annual progress reports and a final report at conclusion of the study will be submitted to the Research Ethics Committee within the required timelines.

14.4 Participant Confidentiality

The study researchers will ensure that the participants' anonymity is maintained. The participants will be identified by a study participant number on the P1vital® ePRO and i-spero® systems. Only the participant consent form and contact details form will include the participant's name, and these will be stored separately from other study data. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the UK Data Protection Act 2018 which requires data to be anonymised as soon as it is practical to do so.

15.0 Expenses, Benefits

Participants will not be reimbursed financially for doing the intervention, for the following reasons:

- All participants may potentially benefit clinically, as participants in both arms will receive the intervention (either immediately or after a delay of 4 weeks).
- We wish for uptake of the intervention to be motivated by clinical benefit (a reduction in intrusive trauma memories) rather than financial benefit, to indicate naturalistic uptake in preparation for roll-out of the intervention.
- No travel expenses are incurred, as the study is run entirely remotely using digital platforms that participants can access from their own home or another preferred location.

However, as an incentive to complete follow-up measures, participants will be offered a £10 online voucher at the end of the study.

16.0 Financial Aspects

The study is funded by Wellcome Trust discretionary project grant award (223016/Z/21/Z) in mental health.

17.0 Use of Information and Publication

All information, including but not limited to scientific research data, generated as a result of this study, are considered confidential and remain the sole property of P1vital and its

academic and pharmaceutical company collaborators. The results of the primary, secondary and tertiary analysis will be reported in a Study Report generated by P1vital Products Ltd (or delegate).

Any anonymised data collected from the intervention use after participants have completed the trial, will only be used to optimise the intervention, and will not be considered research data.

Study results will be also published in peer-reviewed journals and presented at scientific conferences. Study subject identifiers will not be used in any publications.

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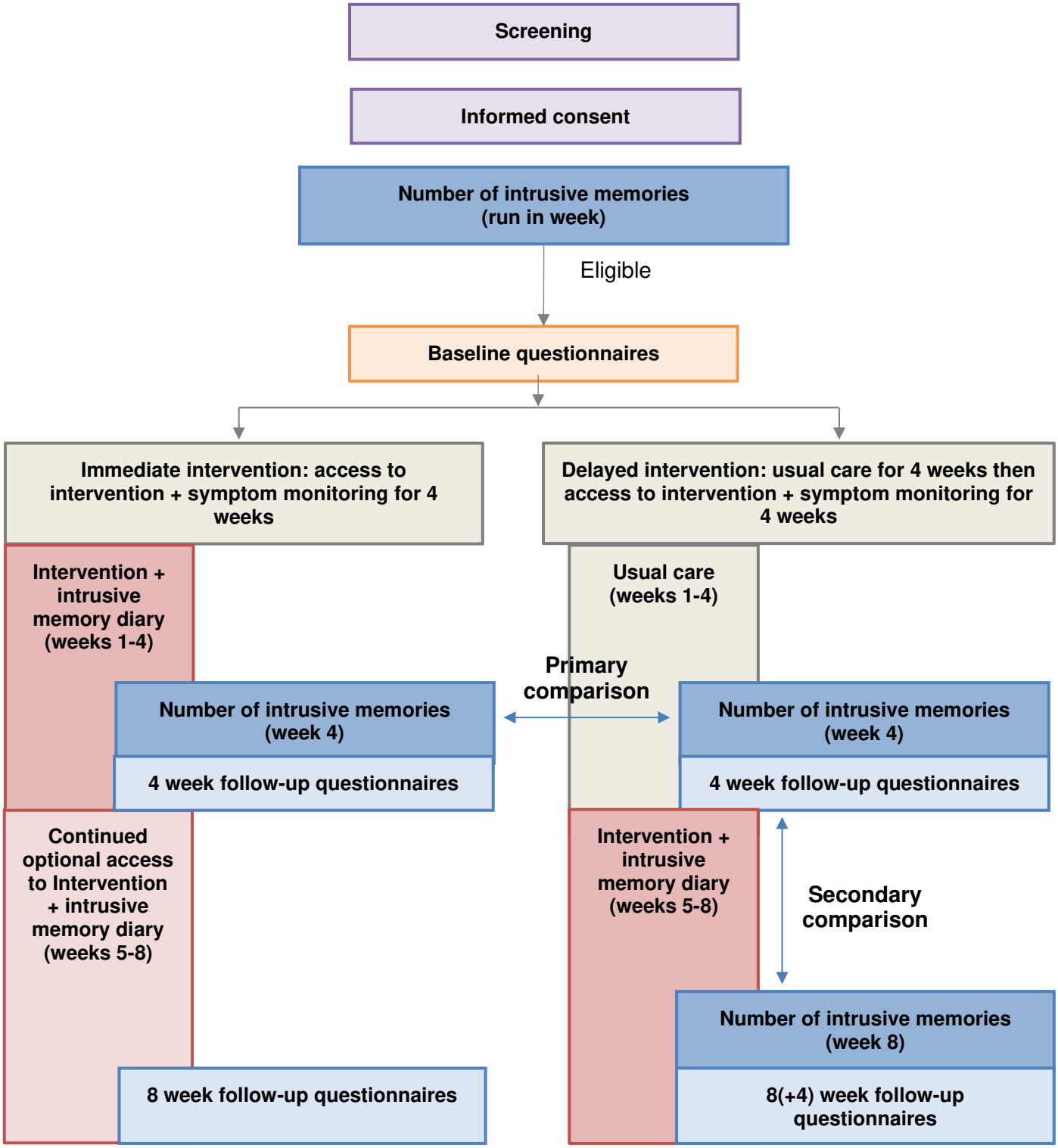
APPENDIX 1: TIME AND EVENT SCHEDULE

Virtual Visit Name	Items	Screening	Run-in week	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Follow Up
Day				**D1**	**D1 to D7**	**D8 to D14**	**D15 to D21**	**D22 to D28**	**D29 to D35**	**D36 to D42**	**D43 to D49**	**D50 to D56**	**D57 to D70**
Visit Window		**D-35**	**D-35 to D-21**	**D-28 to D1**					**D29 + 7days (Del)**	**+7 days (Del)**	**+7 days (Del)**	**+7 days (Del)**	**+7 days (Del)**
Procedures and Assessment Tasks													
Participant information sheet		x											
Eligibility questionnaire	9	x											
Consent form		x											
Inclusion/Exclusion Criteria		x											
Contact details		x											
Intrusive memory diary (daily)			x x x x x x x					x x x x x x x				x x x x x x (Del)	
Intrusive memory ratings	10		x^1					x^1				x^1	
Randomisation				x									
Credibility/Expectancy Questionnaire	6			x									
Demographics	10			x									
Health background	6			x									
Checklist of traumatic events	4			x									
Perceived threat to self/other	2			x									
Peritraumatic Distress Inventory	13			x									
Impact of Event Scale – Revised (IES-R)	22			x				x^2				x^2	
PTSD Checklist for DSM-5 (PCL-5)	4			x				x^2				x^2	

Generalized Anxiety Disorder (GAD-2)	2			x				x^2				x^2	
Patient Health Questionnaire (PHQ-2)	2			x				x^2				x^2	
Sleep Condition Indicator (SCI-08)	8			x				x^2				x^2	
Psychological Outcome Profiles Questionnaire (PSYCHLOPS)	4			x				x^2				x^2	
World Health Organization Disability Assessment Schedule (WHODAS) 2.0	12			x				x^2				x^2	
EQ- 5D-5L (5-level EuroQol 5D)	5			x				x^2				x^2	
Sickness absence	1			x				x^2				x^2	
Scale of Work Engagement and Burnout (SWEBO)	18			x				x^2				x^2	
Support from managers And friend/family	2			x									
Intention To Leave Job	3			x				x^2				x^2	
Changes to health and work	9							x^2				x^2	
Intervention: List of intrusive memories (hotspots)					**x..x(Imm)**				**x..x(Del)**				
Intervention: Distress rating (x3)	**1**				**x..x(Imm)**				**x..x(Del)**				
Intervention: Reactivation Vividness rating	**1**				**x..x(Imm)**				**x..x(Del)**				
Intervention: Playing the computer game Tetris (at least for 20 minutes)					**x..x(Imm)**				**x..x(Del)**				
Intervention: mental rotating rating	**1**				**x..x(Imm)**				**x..x(Del)**				

Record of intrusive memories (daily)					**x..x(Imm)**				**x..x(Del)**				
Feedback questionnaire	**11**							**x^4(Imm)**				**x^4(Del)**	
Qualitative interview (Optional)									x^3				x^3
Note: measures in bold are in i-spero; measures not in bold are in ePRO; Del = delayed-intervention arm, Imm = immediate-intervention arm, X = all participants (immediate and delayed intervention arms)													
1. To be completed by participants at the end of the week (7th day)													
2. Participant for both arms will have a +7 days window to complete week 4 and week 8 outcome measures.													
3. Optional qualitative interview for immediate and delayed intervention arm can be completed within 14 days of day 29 and 57 respectively.													
4. Feedback questionnaire can be completed within 14 days of days 28 and 56 for delayed and immediate intervention arm participants respectively.													

APPENDIX 2: STUDY FLOW CHART



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SIGNATURE CERTIFICATE

REFERENCE NUMBER
9A9DBE1C-A8AA-41A3-A358-543D910CC751

TRANSACTION DETAILS

Reference Number
9A9DBE1C-A8AA-41A3-A358-543D910CC751

Transaction Type
Signature Request

Sent At
03/11/2022 14:02 EST

Executed At
03/17/2022 07:09 EDT

Identity Method
email

Distribution Method
email

Signed Checksum
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Signer Sequencing
Disabled

Document Passcode
Disabled

DOCUMENT DETAILS

Document Name
P1v-Gains-In01 Protocol V7 0 11mar2022

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SIGNERS

SIGNER	E-SIGNATURE	EVENTS
Name Lalitha Iyadurai **Email** liyadurai@p1vital.com **Components** 2	**Status** signed **Multi-factor Digital Fingerprint Checksum** 8b0f839cb9a06f9a0c86b7ac9cff1270915d4796244961ac4b60bddb4e29d0d2 **IP Address** 82.71.43.165 **Device** Chrome via Windows **Typed Signature** Lalitha Iyadurai **Signature Reference ID** FD6B799D	**Viewed At** 03/17/2022 07:08 EDT **Identity Authenticated At** 03/17/2022 07:09 EDT **Signed At** 03/17/2022 07:09 EDT
Name Jonathan Kingslake **Email** jkingslake@p1vital.com **Components** 2	**Status** signed **Multi-factor Digital Fingerprint Checksum** 0e07150d12835e636a8ae08f16b04aa87d1c81a3cb1046cf8a45ceb804361ab1 **IP Address** 86.139.210.18 **Device** Chrome Mobile iOS via iOS **Typed Signature** J Kingslake **Signature Reference ID** E85E758E	**Viewed At** 03/11/2022 14:05 EST **Identity Authenticated At** 03/11/2022 14:05 EST **Signed At** 03/11/2022 14:05 EST

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