Statistical Analysis Plan

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

Descriptive Statistical Analysis Plan (D-SAP)

Final Version 2.0

20 June 2022

Final SAP Date: 20/06/2022

Short Study Title: A brief GAmeplay Intervention for NHS ICU Staff affected by COVID-19 trauma (GAINS Study)

Based on Study Protocol: P1V_GAINS_IN01 Protocol V7.0 11MAR2022

Trial registration: CTR: NCT04992390

Open Science Framework (OSF) Repository osf.io/ep94g

The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents				
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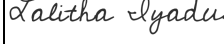
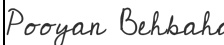
Lalitha Iyadurai	Senior Research Clinical Psychologist	Chief investigator		27/06/2022
Pooyan Behbahani	Project Manager	Clinical Project Manager		23/06/2022
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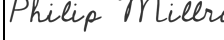
Philip Millroth	Associate Professor in Psychology	Statistical Analyst		23/06/2022
Varsha Ramineni	Statistical Analyst	Statistical Analyst		23/06/2022

Changes from protocol

The table below details changes to the planned analyses in the SAP compared to the protocol which after discussion with the TMG are not considered to require a protocol amendment.

Protocol version and section	Protocol text	SAP version and section	SAP text	Justification

Amendments to versions

Version	Date	Change/comment	Statistician
3.0	23Jun2022	Adding subsection 5.1.2 which includes the reason for including primary outcome compliance measure	Varsha Ramineni
2.0	20Jun2022	Table 3 (primary outcome compliance measure) added to section 5.1	Varsha Ramineni

Additional contributors to the SAP (non-signatory)

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Please note that this Descriptive SAP (the “D-SAP”) describes analyses run at the end of the study, whilst the related Optimisation SAP (the “O-SAP”) called “P1V_GAINS_IN01 Optimisation SAP.pdf” describes the Bayesian analysis approach that will be used throughout data collection.

Abbreviations

Abbreviation	Description
AE	Adverse Event
BF	Bayes Factor
COVID-19	Coronavirus Disease 2019
DMC	Data Monitoring Committee
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
IMs	Intrusive Memories
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
PD	Probability of Direction
PSYCHLOPS	Psychological Outcome Profiles Questionnaire
PTSD	Post-traumatic Stress Disorder
REC	Research Ethics Committee
SAP	Statistical Analysis Plan

SCI	Sleep Condition Indicator
SWEBO	Scale of Work Engagement and Burnout
TMG	Trial Management Group
TSC	Trial Steering Committee
WHO	World Health Organization
WHODAS	World Health Organization Disability Assessment Schedule

Contents

1. Introduction

This document seeks to follow the template and guidelines proposed by Gamble et al. (2017) when analysing and reporting the main results from the current study titled "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", which is shorted as "A brief GAmeplay Intervention for NHS ICU Staff affected by COVID-19 trauma (GAINS Study)". These analyses will explore the efficacy and safety of a brief digital imagery-competing task intervention in comparison with usual care and will be included in the clinical study report, to inform a future definitive clinical trial design.

The purpose of the plan is to:

- Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of a priori and post hoc analyses respectively is appropriate.
- Explain in detail how the data will be handled and analysed to enable others to perform or replicate these analyses.

Bayesian and frequentist analyses were proposed for statistical inference in this study. The Bayesian approach will be used throughout data collection to inform on study design and the details can be found in a separate file named "*P1V_GAINS_IN01 Optimisation SAP.pdf*". The present document (the "D-SAP) will present the details for all frequentist analysis in line with the analysis specified in study protocol.

Additional exploratory or auxiliary analyses of data not specified in the protocol may be included in this analysis plan. This analysis plan will be made available in a public platform before the trial database is locked for the final analysis. Additional analyses suggested by reviewers or editors will be performed if considered appropriate. This will be documented in a file note. Amendments to the statistical analysis plan will be described and justified in the final report of the trial and where appropriate in publications arising from the analysis.

Other health economic and qualitative analysis plans are beyond the scope of this document. Note the quantitative part of the Intervention Feedback questionnaire will be analysed (See Section 5 for details).

1.1 Background and rationale

Intensive care unit (ICU) staff are frequently exposed to traumatic events at work (e.g., witnessing patients die), amplified by the COVID-19 pandemic. A significant proportion experience intrusive memories (or “flashbacks”) of these events that pop suddenly into mind: these imagery-based memories can disrupt functioning and contribute to posttraumatic stress disorder. Previous research has shown that a brief behavioural intervention can reduce the number of intrusive memories after a traumatic event.

In this study we aim to optimise a brief digital intervention to help reduce the number of intrusive memories (primary outcome) experienced by ICU staff.

We will explore if it can improve clinical, work functioning and wellbeing measures (secondary outcomes).

We will recruit up to 150 staff with intrusive memories of events experienced whilst working in an ICU during the COVID-19 pandemic.

1.2 Objectives

The main objective is to optimise a brief digital intervention to help reduce the number of intrusive memories experienced by staff who worked in an ICU during the pandemic (primary outcome). The process is that interim analyses for the primary outcome will be used to guide study optimisation and assess evidence for early stopping of the trial (detailed in the *P1V GAINS IN01 Optimisation SAP*). This means that the intervention can evolve and improve over the course of the trial and will be used to inform the next trial.

Once the trial has concluded, a standard analysis will be conducted as described in this SAP (of the type that may be used in the next trial).

The primary objective of this trial is 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). See Section 2.1 for details of the trial design.

The secondary objectives of this trial are:

- 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).

The tertiary objectives of the trial are:

- To assess 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 (assessed qualitatively: not included in this SAP).

- 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 (assessed qualitatively: not included in this SAP).

2. Study methods

2.1 Trial design

The study is a two arm, parallel group, 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:

- **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 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 (i.e., including maximum allowable time-windows for assessments).

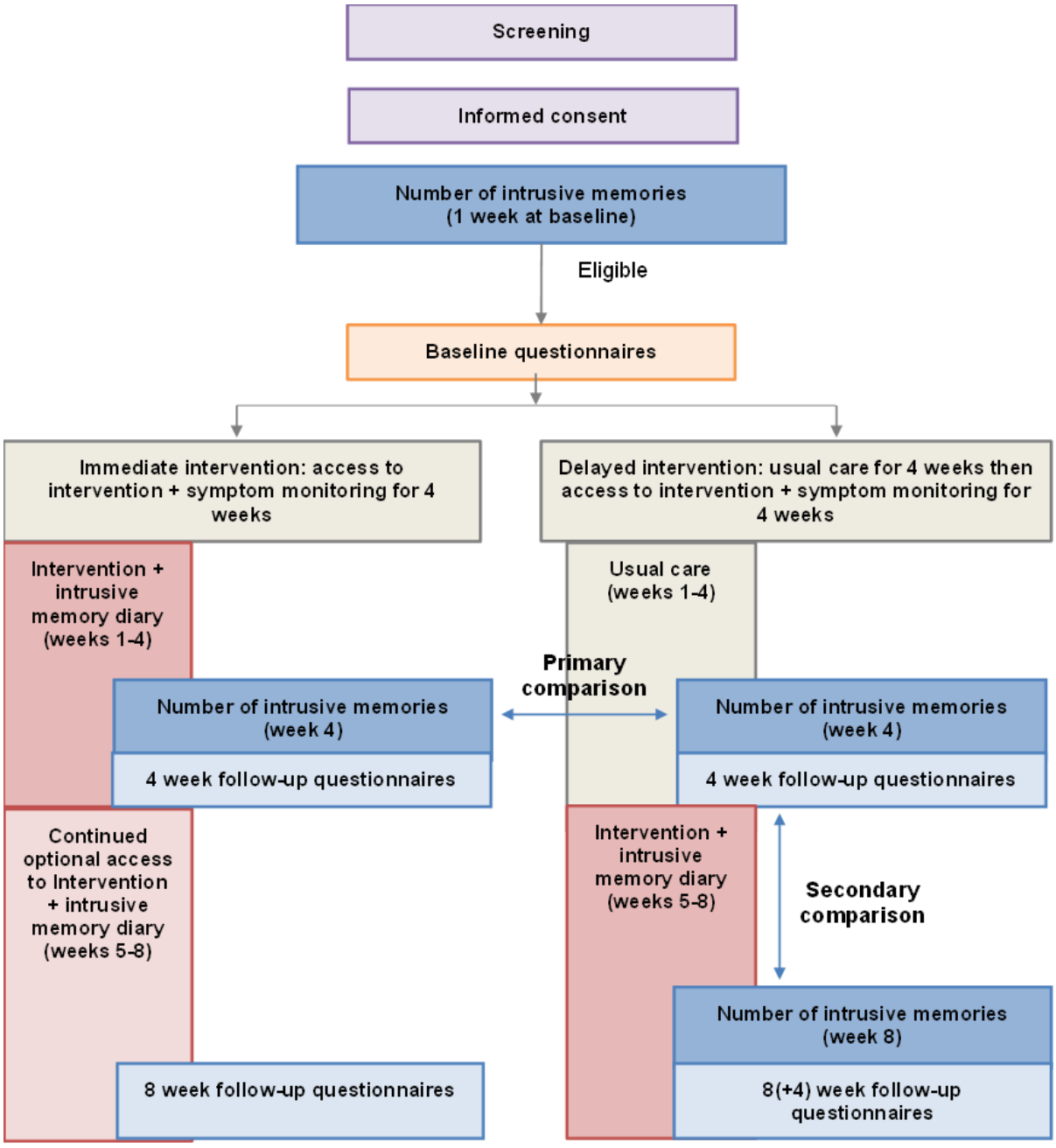
There will be virtual visits (i.e., audio or video calls between participant and researcher) at screening, on first intervention day, for optional qualitative interview, and to provide support with additional intervention sessions or assist the participant (e.g., with outcome completion) when appropriate. Remote participant assessments (i.e., typically without researcher; online questionnaires only) will take place at Baseline, 4 and 8 weeks.

The study will enrol up to approximately 150 participants, 75 participants per study arm. This study may conclude early i.e., before reaching the max 150 participants (Please refer to *P1V GAINS IN01 Optimisation SAP* for details on early stopping of the trial). 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.

Please see study flow chart below representing the overall trial design:

Figure 1: STUDY FLOW CHART



2.2 Randomisation & Blinding

2.2.1 Randomisation

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% 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 P1vital® ePRO (a secure web-based clinical research system) to ensure that allocation cannot be influenced by the research team (i.e. randomisation is computerised and automated to ensure allocation concealment).

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

2.2.2 Blinding

Statisticians will be blinded to allocation, and all assessments are self-report questions 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.

2.3 Sample size

This study uses an adaptive Bayesian design for speed under pandemic conditions to inform a future definitive RCT design (Schönbrodt and Wagenmakers, 2018; Stallard *et al.*, 2020). For details on the final sample size, please see the *P1V GAINS IN01 Optimisation SAP.*

We plan to recruit up to approximately n = 150 into this study, as stated in the grant application with the potential to end recruitment earlier based on the results of the interim analyses.

The choice of maximum sample size was initially informed by power estimates based on an effect size of $d = 0.63$ for the primary outcome, pooled from three previous RCTs of this intervention (Horsch *et al.*, 2017; Iyadurai *et al.*, 2018; Kanstrup *et al.*, 2021)

2.4 Framework

The primary objective of the study is 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.

The secondary objective is to test the effectiveness of immediate intervention over delayed intervention on various secondary outcomes. Both primary and secondary outcomes are testing for superiority.

2.5 Statistical interim analyses and stopping guidance

It was planned that the frequentist statistical approaches will be conducted at the end of the study to analyse the primary and secondary outcomes.

Interim analyses and stopping guidance are covered in the *P1V GAINS IN01 Optimisation SAP.* It states that interim analyses will be conducted at a group level (immediate intervention vs delayed intervention) starting with a small number of participants (e.g. n=20) and every approximately between 4-10 participants thereafter, up to a maximum of approximately n=150. If there is strong evidence (i.e.

Bayes Factor > 20) for no benefit of the intervention (i.e. that those in the immediate intervention arm, compared to the delayed intervention arm, have a greater number of intrusive memories) then early stopping of the trial will be considered. If we see strong evidence that the intervention is more effective than control (i.e. that those in the immediate intervention arm, compared to delayed intervention arm, have fewer intrusive memories) before reaching the max n =150 participants, this is deemed sufficient evidence for the effectiveness of the intervention to consider concluding the trial early. *Please refer to the P1V GAINS IN01 Optimisation SAP for full details.*

2.6 Timing of final analysis

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.

The frequentist analysis will be conducted once 8 weeks data available on an intention to treat (ITT) basis

2.7 Timing of outcome assessments

Briefly, data from all randomised patients will be collected at baseline, 4 weeks follow-up and 8 weeks follow-up time. The schedule of study procedures for all data collection is given in Section 5.1.

3 Statistical Principals

3.1 Confidence intervals and P values

All applicable statistical tests in frequentist modelling will be 2-sided and will be performed using a 5% significance level. No multiplicity adjustments will be undertaken as there is only one primary outcome, and analysis for secondary outcomes aim to support primary analysis results (European Medicines Agency, 2016).

3.2 Adherence and protocol deviations

Definition of adherence to the intervention:

During the first guided session, the participant completes all key components of the intervention including: accurately identifying and briefly listing intrusive memories; choosing an intrusive memory to target; *briefly* bringing to mind the intrusive memory image before gameplay (sufficiently clearly but not so much it becomes overly upsetting); *then* sufficient uninterrupted Tetris game play (c.20 min in total; range 15-25 min); during gameplay actively using mental rotation. Non-adherence may be indexed by in session reports or behaviours that are incompatible with the steps above e.g. deliberately bringing the memory to mind repeatedly during game play. (Technical problems which were resolved in some way such as not being able to view the video instructions for steps in the study procedure (and instead reading the written transcript), intervention glitches or internet connection problems which do not disturb prevent key components from being completed are not considered protocol deviations. Similarly, minor interruptions during gameplay which do not disturb overall engagement in the game will not be considered a protocol deviation). In cases where adherence is unclear, a case discussion will be held.

Adherence to the intervention will be presented as the number (%) of participants who adhered to the intervention by treatment group.

Definition of protocol deviations:

A full list of protocol deviations will be denoted prior to unblinding of treatment including:

1. Non-completion of the primary outcome measure
2. Non-completion of guided intervention session/non-adherence to the intervention (as defined above).

All protocol deviations will be summarised, using the number (%) of participants by treatment group with details of type of deviation provided. The patients that are included in the ITT analysis data set will be used as the denominator to calculate the percentages. No formal statistical testing will be undertaken. Protocol deviations are classified prior to unblinding of treatment. A blinded list of protocol deviations will be shared with the statistician after the data base lock is reached.

3.3 Analysis populations

All analyses will be conducted on an intention to treat (ITT) basis. The ITT is defined as all randomised participants. The per-protocol analysis set consists of subjects for whom there are no significant adherence and protocol deviations according to the definition in previous Section 3.2. The Per Protocol Population (PP) are used for sensitivity analyses and will be defined at the Data Review Meeting.

4 Trial population

4.1 Screening data

The number of patients screened will be presented in CONSORT diagrams.

4.2 Eligibility

The number of ineligible patients randomised, if any, will be reported, with reasons for ineligibility and presented in CONSORT diagrams.

4.3 Recruitment

A CONSORT flow diagram will be used to summarise the number of patients who were:

- assessed for eligibility at screening
    - eligible at screening
    - ineligible at screening*
- eligible and randomised
- eligible but not randomised*
- received the randomised allocation
- did not receive the randomised allocation*
- randomised and included in the primary analysis
- randomised and excluded from the primary analysis*

*Reason will be provided in CONSORT Diagram.

4.4 Withdrawn/follow-up

The numbers (with reasons) of losses to follow-up (drop-outs and withdrawals) over the course of the trial will be summarised by treatment arm and presented in CONSORT diagram.

4.5 Baseline patient characteristics

Participants will be described with respect to 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 information, and other characteristics (see Table 1 below) at baseline, both overall and separately for the two randomised groups. The details of descriptive statistics are reported in 5.2.1. Tests of statistical significance will not be undertaken for baseline characteristics; rather the clinical importance of any imbalance will be noted (European Medicines Agency, 2013).

Table 1: Summary of the baseline measures

Baseline measure	Scale description	Items & scoring
Credibility/Expectancy Questionnaire	This 6-item questionnaire will assess participants' belief that the intervention will help reduce their intrusive memories	Items 1, 2, 3 and 5 rated on a 9-point ordinal scale from 1 (not at all) to 9 (very). Items 4 and 6 rated on a 11-point ordinal scale from 0% to 100% (in 10% increments). Scores on items 4 and 6 were transformed with a minimum of 1 and a maximum of 9, and a total score ranging 6 to 54 was calculated.
Demographics	8 item questionnaire assessing: 1. Age (in years) 2. gender identity 3. education level 4. marital status 5. ethnicity 6. employment status 7. number of hours per week currently working 8. number of years working as a healthcare professional	1. Number 2. Categorical response (7 options) 3. Categorical response (6 options) 4. Categorical response (6 options) 5. Open text response (which has been categorised into 19 groups) 6. Categorical response (7 options) 7. Number 8. Number
Health background	6-item questionnaire to assess: 1. current physical health problems 2. current treatments/medication for physical health problems 3. current/past mental health problems 4. current treatments/medication for mental health problems 5. family history of mental health problems	1, 2 and 4 rated Yes/No (binary response), and if the participant responds Yes, they are asked to give brief details (open text response). 3 rated Yes/No (binary response), and if the participant responds Yes, they are asked to list the mental health problems (open text response) and indicate Past/Current (binary response) for each. 5 rated Yes/No (binary response), and if the participant responds Yes, they are asked to list

	6. prior traumatic events	the mental health problem and the family member. 6 is rated Yes/No (binary response) for a series of 14 traumatic events
Checklist of traumatic events	4-part questionnaire assessing a) the types of traumatic events experienced or witnessed during the COVID-19 pandemic, b) the time frames in which those events occurred, c) the number of work-related traumatic events experienced/witnessed during Covid-19, and d) the number of traumatic events that were not work-related that were experienced/witnessed during Covid-19.	a) Scored as 0 (no) or 1 (yes) for a series of 10 different types of traumatic event b) Scored as 0 (no) or 1 (yes) for 5 different time frames c) Number response d) Number response
Perceived life threat to self-other	2-item questionnaire assessing the extent to which the participant felt their life or someone else's life was in danger during the worst traumatic event	Both items rated on a 10-point ordinal scale from 0 (not at all) to 10 (extremely)
Peritraumatic Distress Inventory	This 13-item measures the extent to which participants experienced a number of emotional reactions during the trauma	Items are rated on a 5-point ordinal scale from 0 (not at all) to 4 (extremely) and a total score is calculated.
Support from managers and friends/family	2-item questionnaire, participant rates how well supported they have been by their supervisors/managers and their family/friends	Both items rated on a 5-point ordinal scale: "not at all", "a little bit", "moderately", "quite a bit", "extremely"

5 Analysis

5.1 Outcome definitions

5.1.1 Primary, Secondary, and Tertiary Outcomes

The number of intrusive memories of traumatic event(s) are recorded by participants in a brief daily diary for 7 days during the run-in week (Day 0 to 6) and week 4 (Day 22 to 28) of the intervention. The primary endpoint is the total number of intrusive memories of traumatic event(s) reported in week 4 (i.e. from Day 22 to 28 post first intervention session in immediate intervention arm or equivalent time frame in delayed intervention arm). We are interested in the between-groups comparison while controlling for number of intrusive memories during the run-in week.

Table 2: Summary of the outcome measures

Outcome measure	Scale description	Items & scoring	Baseline	Week 4	Week 8
Primary endpoint					
Number of intrusive memories of traumatic event(s)	Number of intrusive memories of traumatic event(s) recorded by participants in a brief diary daily for 7 days.	Total number of intrusive memories of traumatic events reported in Week 4 (between-groups comparison controlling for number of intrusive memories during the run-in week).	X	x	
Secondary endpoints					
Number of intrusive memories of traumatic event(s)	Number of intrusive memories of traumatic event(s) recorded by participants in a brief diary daily for 7 days.	Total number of intrusive memories reported in Week 4 compared to run-in week for the immediate group and Week 8 compared to Week 4 for the delayed group (within-group comparisons).	X	x	x
Intrusive memory ratings	8 items assessing aspects of intrusive memories: 1. Frequency in past week 2. Distress 3. Disruption to concentration 4. a) Interference with what you were doing b) Duration of interference with what you were doing 5. Impact on work functioning 6. In what ways impacted on work functioning 7. Impact on functioning in other areas of life 8. In what ways impact on functioning in other areas of life	Items are examined separately (not summed) and scored as follows: 1. 7-point categorical response from 'never' to 'many times a day' 2. 11-point ordinal response from 'not at all' (0) to 'extremely' (10) 3. 11-point ordinal response from 'not at all' (0) to 'very much (10) 4. a) 11-point ordinal response from 'not at all' (0) to 'very much (10) b) 6-point categorical response from '<1min' to '+60mins' 5. 11-point ordinal response from 'not at all' (0) to 'very much (10) 6. Open text response (will be analysed qualitatively – not included here) 7. 11-point ordinal response from 'not at all' (0) to 'very much (10) 8. Open text response (will be analysed qualitatively – not included here)	X	x	x
Impact of Event Scale – Revised (IES-R)	This 22-item questionnaire assesses subjective previous 7 days distress after a traumatic event.	22 items with 5-point ordinal response; has intrusion, avoidance and hyperarousal subscales and total score. We will analyse total score (mean of all 22 items) and subscales separately (mean of items in each subscale).	X	x	x

PTSD Checklist for DSM-5 (PCL-5)	It is shortened 4-item version of the PCL-5 assesses symptoms of PTSD over the last month.	4 items with 5-point ordinal response from 'not at all' (0) to 'extremely' (4); total score ranges from 0 to 16 (cut-off for possible PTSD is 10 or above).	X	x	x
Generalized Anxiety Disorder (GAD-2)	2 items drawn from the GAD-7 Scale. This 2-item self-report measure assesses the severity of anxiety symptoms in the previous two weeks.	2 items with 4-point ordinal response from 'not at all' (0) to 'Nearly every day' (3); total is the sum of both items and ranges from 0 to 6 (cut-off for possible GAD is 3 or above).	x	x	x
Patient Health Questionnaire (PHQ-2)	The 2 items were drawn from PHQ-9 Scale. This 2-item short-form self-report measure assesses symptoms of previous two weeks depression	2 items with 4-point ordinal response from 'not at all' (0) to 'Nearly every day' (3); total score is the sum of both items and ranges from 0 to 6 (cut-off for possible major depressive disorder is 3 or above).	x	x	x
Sleep Condition Indicator (SCI-08)	This 8-item scale measures sleep problems against the DSM-5 criteria for insomnia disorder.	8 items are each scored 0-4. Total score ranges 0-32, with a higher score indicating better sleep (individual item scores ranging from 0 to 2 indicate possible threshold criteria for insomnia disorder).	x	x	x
Psychological Outcome Profiles Questionnaire (PSYCHLOPS)	This measure consists of 9 questions designed to assess the impact of a person's problems over the past week; participants are asked to think about problems specifically in relation to their intrusive memories.	4 items are scored; the other items are free text responses or may provide additional information about the person's problems (and may be analysed qualitatively – not included here). Questions 1b, 2b, 3b, and 4 are scored. These have a six-point ordinal scale ranging from 0 to 5 and are summed to generate a total score from 0 to 20. Higher values indicate the person is more severely affected.	x	x	x
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 due to health conditions over the past 30 days.	12 items are scored on a 5-point ordinal scale from 'no difficulty' (0) to 'extreme difficulty or cannot do' (4). The overall score is calculated as a percentage of the sum of each item score / the maximum possible score (i.e., 48 points).	x	x	x
EQ- 5D-5L (5-level EuroQol 5D)	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	5 items are scored on a 5-point ordinal scale from 'no problem' (1) to 'highest level of problems' (5). Respondents also rate their overall health today from 0 (the worst health you can imagine) to 100 (the best health you can imagine). Scores are analysed separately (not summed).	x	x	x
Sickness absence	A single item will assess the number of sick days taken from work during the past 4 weeks.	Total number of sick days.	x	x	x
Scale of Work Engagement and Burnout (SWEBO)	This 19-item self-report measure assesses work engagement and burnout.	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	x	x	x

		calculated for two subscales: engagement and burnout.			
Intention to Leave Job	3 items are used to assess participants' intention to leave their job e.g. "I think a lot about leaving the job",	3 items 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.	x	x	x
Weekly Work Pattern	Two items asses the number of days worked and number of night shifts worked in the last week.	Both with responses from 0 to 7. Items are examined separately (not summed).	x	x	x
Tertiary endpoints					
Changes to Health and Work	9 items assessing 1. the experience of new work-related traumatic events; 2. the types of new work-related traumatic events 3. the number of new work-related traumatic events 4. the number of new non-work related traumatic events 5. the experience of any additional stressful life events; 6. receipt of any new treatments; 7. untoward medical occurrences; 8. change of job; 9. change of hours	Items 1, 5, 6, 7, 8 and 9 are scored 0 (no) or 1 (yes). Item 2 is scored as 0 (no) or 1 (yes) for a series of 10 different types of traumatic event. Items 3 and 4 are numerical count responses. (Note: if participants responds "yes" to items 5 to 9, they are asked to give brief details - open text response, which may be analysed qualitatively – not included here)		X	X
Feedback Questionnaire	5 items assessing how easy, helpful, burdensome, distressing and acceptable participants found the intervention. 3 items assessing how willing they would be to use the intervention in the future, how confident they would be in recommending it to a friend, and how much they feel the intervention could be used in NHS Trusts/healthcare organisations.	8 items rated on 11-point ordinal scale from 0 (not at all) to 10 (very) (Note: 4 additional open response text items will be analysed qualitatively – not included here)		X (imm)	X (del)

Note. imm = immediate intervention arm, del = delayed intervention arm

5.1.2 Measurement and Accuracy of Outcomes

The endpoint 'Number of intrusive memories of traumatic event(s)' is recorded by participants in a brief intrusive memory diary daily for 7 days. Each day, the participant is asked to indicate if they have had any intrusive memories (yes/no) and if so, how many. 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).

The diary accuracy rating measure (see Table 3) will be summarised along with all demographic, baseline and outcome measures as described in Section 5.2.1. This will be used for comparability with previous research.

Table 3: Primary outcome compliance measure

Outcome measure	Scale description	Items & scoring	Baseline	Week 4	Week 8
Diary accuracy rating	Single item assessing self-reported accuracy of completing the 7-day intrusive memory diary	11-point ordinal scale from 0 (not at all accurately) to 10 (extremely accurately)	X	X	X

5.2 Analysis methods

All primary and secondary analyses will be conducted on an intention to treat (ITT) basis (European Medicines Agency, 2015). The ITT is defined as all randomised participants. Single level generalised linear modelling will be performed for the primary analysis and multilevel modelling (MLM) will be performed for secondary analyses to quantify the treatment effect, and its precision on all outcome measures. The details on descriptive statistics for all variables, frequentist analytical modelling for primary outcome and secondary outcomes are presented here in this section.

Qualitative analysis plans are beyond the scope of this document.

5.2.1 Summary of baseline information and outcomes measure

All patient demographic, baseline and outcome measures will be summarised by arm, and across follow-up times if repeatedly collected, with n (non-missing sample size), mean, standard deviation, median, maximum and minimum for continuous variables, the frequency and percentages (based on the non-missing sample size) of observed levels for all categorical measures.

The recruitment rate and attrition rate will be calculated.

5.2.2 Testing the treatment effects for primary outcome

To quantify treatment effect estimate and its 95% CI on primary outcome, Poisson regression will be performed with baseline measure and binary arm status included as fixed effect covariates. Zero inflated Poisson (ZIP) will be performed if there are extreme 0 counts or negative binomial model will be conducted if the data is over dispersed, with reference to data exploratory results (see Blasco-Moreno *et al.*, 2019).

For the Poisson generalised linear model to model the total number of intrusive memories recorded in week 4 using a canonical link function (logarithm), Let n be the number of participants which we are analysing, then for each participant $i = 1,\ldots,n$ we denote:

- Y_i to be the random variable representing the primary endpoint (total number of intrusive memories in week 4).
- $Baseline_i$ to be the total number of intrusive memories recorded during the run-in week.
- ARM_i to represent whether the participant is in the immediate intervention arm or the delayed intervention arm (control arm).

The model is as follows, where α, β_1, β_2 are our unknown model parameters.

$$\mathrm{Y_i} \sim \mathrm{Poisson}(\mu_i)$$

$$\log(\mu_i) = \alpha + ARM_i\beta_1 + Baseline_i\beta_2$$

5.2.3 Sensitivity analysis for primary outcome

Following sensitivity analyses will be conducted to check the robustness of the treatment effect estimate:

a. Model shown in Section 5.2.2 will be performed on observed data only.

b. Observation-level random effects (OLRE) Poisson model for over dispersed count data with reference on data exploratory results: OLRE Poisson model includes a random intercept (treat the participant number as a random effect) if any significant variability is shown from model exploring. The OLRE model is detailed below where γ_{0i} is the random effect for the intercept for each participant i that accounts for the participant-specific variation in the primary endpoint. The random-effects intercepts γ_{0i} are drawn from a normal distribution with mean 0 and variance $\sigma^2_{\gamma_0}$ which is estimated by the model.

$$log(\mu_i) = \alpha_i + ARM_i\beta_1 + Baseline_i\beta_2$$

$$\alpha_i = \alpha + \gamma_{0i}$$

$$\gamma_{0i} \sim N\left(0, \sigma^2_{\gamma_0}\right)$$

c. Outliers will be identified through inspection of residual plots and Cook's distance vs leverage plots. If any outlier(s) are identified, results using data without outliers will be presented as sensitivity analysis.

5.2.4 Secondary analysis for primary outcome

Model shown in Section 5.2.2 will be performed on per protocol population.

5.2.5 Analysis of secondary outcomes

To quantify treatment effect estimate and within arm change between each measuring time for the number of intrusive memories at week 8 and other secondary outcome measures. MLM will be performed with baseline measure, binary arm status, following up time and interaction of arm × time included as fixed effect covariates, participant as level 2 analytical units (European Medicines Agency, 2013). ML linear regression will be used for normally distributed continuous data (Vickers and Altman, 2001), ML logistic regression will be used for binary outcomes. Multilevel Poisson regression will be performed for count data. Skew continuous measure will be transformed for ML linear regression model if needed with reference on data exploratory results, (see for example Manning and Mullahy, 2001; Ives, 2015; Curran-Everett, 2018). For count data, ZIP model will be performed if there are extreme 0 counts or negative binomial model will be conducted if the data is over

dispersed. The treatment effect estimate and its 95% CI together with significance level for between group comparison will be derived from MLM, the estimate and its 95% CI will be presented for the estimate of within group change from baseline to each follow-up time.

If MLM result showed non-significant level-two variance estimate, or any model convergence issues, conventional single level regression will be performed with cluster-robust standard error reported for treatment effects estimate.

5.2.6 Summary of table and figures

A summary of tables and figures is provided as additional information to accompany the analyses specified in this SAP. At a minimum, analyses will be summarized and presented in three tables and two figures.

The first table will involve a summary of all participant demographic and baseline characteristics with n (non-missing sample size), mean, standard deviation, median, maximum and minimum for continuous variables, the frequency and percentages (based on the non-missing sample size) of observed levels for all categorical measures.

The second table will involve data for the total number of reported intrusive memories for the three time points (run-in week, Week 4, Week 8), with n (non-missing sample size), mean, standard deviation, effect sizes for continuous variables (effect size (Cohen's d, with 95% confidence intervals). This will be accompanied with a figure illustration for the primary outcome measure (Week 4).

The third table summarize secondary and other outcome measures by arm, and across follow-up times if repeatedly collected (e.g., 4 weeks, 8 weeks), with n (non-missing sample size), mean, standard deviation, median, maximum and minimum for continuous variables, the frequency and percentages (based on the non-missing sample size) of observed levels for all categorical measures.

A CONSORT diagram will be provided to illustrate the number of participants involved in each phase and of the trial (e.g., enrolment, intervention allocation, completion of primary- and secondary outcomes and follow-ups).

5.3 Missing data

Exploratory data analysis will be used to assess the level of missing data for each participant. As the intrusive memory diary data is collected sequentially over time (either at baseline or at week 4), we will use time series methods (e.g. Chatfield, 2003) and an expectation-maximisation algorithm (Dempster, Laird and Rubin, 1977) to impute missing values (see also National Research Council., 2010) .

Initial missing values will be imputed by taking expectations across a participant's available diary data. Using Poisson likelihood and correlated errors, we maximise over this 'full' data set to provide updated expected values for the missing data. We will iterate over these latter steps until convergence in values of missing data (to a pre-determined threshold) is achieved.

5.4 Additional analyses/exploratory analysis

No other analyses were planned.

5.5 Harms & Adverse events

The number (percentage) of patients experiencing each AE/SAE will be presented for each treatment arm categorised by severity (across follow-up time) (Ioannidis *et al.*, 2004). For each participant, only the maximum severity experienced of each type of AE will be displayed. The number (percentage) of occurrences of each AE/SAE will also be presented for each treatment arm. No formal statistical testing will be undertaken (Phillips, Sauzet and Cornelius, 2020).

5.6 Statistical software

For all descriptive statistics and modelling for all outcomes, Stata and R, will be used. The scripts for the final analysis will be made available on the Open Science Framework to reviewers prior to publication and be made publicly available after the main paper(s) have been published. All the software will use the latest version available in University of Nottingham (UoN) when study data is ready for analysis. All the data will be stored in UoN secure server and analysed in computers located in

UoN. All the data and analytic code will be archived as per instruction from study PI Dr Lalitha Iyadurai & Sponsor Mr Jonathan Kingslake who will be the data custodian for this study.

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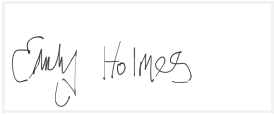

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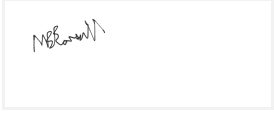

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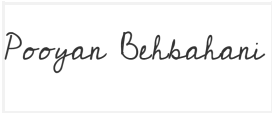

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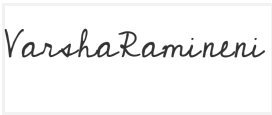

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