Study Title: Treating 'felt sense of anomaly'-type dissociative experiences by targeting hypothesised psychological maintenance mechanisms: A Single Case Experimental Design series

Internal Reference Number / Short title: Dissociation CBT Studies (DisCS).

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Sponsor:	University of Birmingham
Funder:	University of Birmingham School of Psychology

Conflicts of Interest: None to declare.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee and Regulatory Authorities unless authorised to do so.

Sponsor statement:

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

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1. LAY SUMMARY

Why is the research important?

Dissociation involves distressing feelings of unreality and disconnection. Evidence suggests it is particularly common amongst people with existing mental health difficulties, where it has been linked with greater clinical severity, poorer treatment response, and increased self-harm and suicidality. However, there are currently no psychological treatments for dissociation that have been developed from a scientific understanding of its underpinning psychological factors. We would like to develop such a treatment. Previous research has identified potential factors, and we have developed three brief psychological interventions each targeting one factor. By precisely targeting a factor with therapy, any resulting 'downstream' effect on dissociation would indicate that the relationship between the factor and dissociation is causal – not just correlational. This case series will therefore test whether three factors (cognitive appraisals; worry; difficulties tolerating emotions) have a causal relationship to dissociation. This information will be crucial for building a case for support to fund larger, more rigorous tests of the factors and interventions.

What will happen in the study?

Three studies, each with four participants, will test a different psychological factor. Participants will be: adults (16+ years); on a waiting list for NHS psychological therapy; high scorers on a dissociation questionnaire. Participants will complete assessments before and after treatment, and at a one-month follow-up. The studies follow a 'multiple baseline design', meaning that all four participants for that study will complete their baseline assessment in the same week, and then be randomly allocated to wait either one, two, three, or four weeks before starting the intervention. The intervention will consist of four therapy sessions taking place within a five-week 'window'. Taking part in the research is voluntary. Before deciding whether to participate, we will explain the study and answer any questions.

How will results be measured?

Daily, participants will record a score for their dissociation and the psychological factor being targeted. At baseline, post-therapy, and follow-up we will also measure their levels of other factors related to dissociation (i.e. those not targeted by the therapy). Additionally, we will request feedback from participants about the therapy at the end of their involvement, in order to improve it in future.

Ultimately, if successful, these interventions could form a pilot therapy for further testing and development. We hope this would mean fewer people struggle with the challenges of dissociation.

2. SYNOPSIS

Study Title	Treating 'felt sense of anomaly'-type dissociative experiences by targeting putative psychological maintenance mechanisms: A Single Case Experimental Design series.		
Internal ref. no. (or short title)	Dissociation CBT Studies (DisCS).		
Study pre-registration	Intended registry: ClinicalTrials.gov		
Sponsor	University of Birmingham		
Funder	University of Birmingham School of Psychology via new starter fund awarded to EČ.		
Clinical Phase	Phase 1: Single case study / case series		
Study Design	Multiple baseline single case experimental design (x3).		
Participants	Adults (age 16 and above) awaiting psychological therapy in NHS mental health services with high levels of dissociation.		
Sample Size	12 (4 per study)		
Planned Study Period	Total study period: 6th March 2023 – 5th March 2024. Individual participant involvement: 12-15 weeks.		
Planned Recruitment Period	6th March 2023 – 31st December 2023.		
	Objectives	Outcome Measures	Timepoint(s)
Primary	To determine whether the psychological intervention reduces the psychological maintenance mechanism (factor) of interest (i.e. cognitive appraisals [study 1]; perseverative thinking [study 2]; affect intolerance [study 3]).	Study 1: CAD-P Study 2: PTQ Study 3: AIS	Daily rating (throughout baseline and intervention window), every other day (throughout follow-up window).
Secondary	To gain a preliminary indication of whether the relationship between the proposed psychological factor (cognitive appraisals; perseverative thinking; affect intolerance) and 'felt sense of anomaly'-type dissociation is causal.	As above + ČEFSA-14	As above.
Qualitative	To improve the therapy intervention for use in future treatment development studies.	Qualitative feedback from participants.	At one-month follow-up.
Intervention	Study 1 (cognitive appraisals): CBT techniques for cognitive reappraisal. Study 2 (perseverative thinking): Condensed form of Wells' CBT intervention for worry (negative ruminative thinking). Study 3 (affect intolerance): ACT techniques for approaching and tolerating affect.		
Comparator	Through the study design, the participants serve as their own comparator (baseline [A] versus therapy [B] phase), and random allocation of the length of the baseline ('multiple baseline design') allows each participant to be the comparator to the others in that study (testing that maturation is not the cause of any improvement seen in the B phase).		

3. ABBREVIATIONS

AE	Adverse Event
AIS	Affect Intolerance Scale[1]
AMHT	Adult Mental Health Team
CAD-P	Cognitive Appraisals of Dissociation in Psychosis scale[2]
CBT	Cognitive Behavioural Therapy
ČEFSA-14	Černis Felt Sense of Anomaly Scale (Short Form) (Černis et al., *in prep*)
CI	Chief Investigator
CRF	Case Report Form
DBT	Dialectical Behavioural Therapy
EIP	Early Intervention in Psychosis
FSA	Felt Sense of Anomaly
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GSE	General Self Efficacy scale[3]
HRA	Health Research Authority
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IP	Intellectual property
LEAP	Lived Experience Advisory Panel
MBD	Multiple Baseline Design
NHS	National Health Service
OAS	Online Alexithymia Scale (amended)[4]
PIS	Participant/ Patient Information Sheet
PTQ	Perseverative Thinking Questionnaire[5]
REC	Research Ethics Committee
RTD	Responses to Dissociation scale[4]
SAE	Serious Adverse Event
SCED	Single Case Experimental Design
UoB	University of Birmingham
VAS	Visual Analogue Scale

4. BACKGROUND AND RATIONALE

What is dissociation?

"I was in a totally different world; it was going on all around me. I thought that I might have died and was in hell, and I was thinking maybe that's what it was." *-- "Maria"*

Dissociation involves confusing and upsetting feelings of unreality, unfamiliarity, or disconnection in relation to your mind, body, or surroundings[6]. For example, some people describe being detached from their own emotions, including affection for loved ones, or feeling profoundly 'strange', as though they are living life from behind a thick pane of glass. These experiences can cause significant distress[6,7], and have been linked with risk of self-harm or suicide[8–10], and with increased severity[11] and incomplete treatment-response[12] of comorbid mental health diagnoses. Many dissociative experiences considered transdiagnostic[13,14]. For example, dissociation is present at a very high rate in psychotic disorders (potentially up to 50%[15]). Crucially, in this context, it may even be instrumental in the development and maintenance of key psychotic symptoms, such as paranoid delusions and auditory hallucinations[16].

However, dissociation has traditionally been considered within the context of post-traumatic responses. As a result, a fuller understanding of dissociation as an independent construct – rather than simply as another post-traumatic symptom – has yet to be achieved.

This 'neglect'[17], and extensive debate within the field[18], has also resulted in a lack of clarity about the precise accepted definition of 'dissociation' as a construct[19,20]. Therefore, in previous work, we delineated a subgroup of common dissociative experiences unified by a core phenomenological experience of a 'felt sense of anomaly' (FSA)[6,21]. We will operationalise the term 'dissociation' within this project by focusing on this specific type of dissociative experiences (FSA-dissociation), since this has been demonstrated to be common and transdiagnostic[22,23].

What are the psychological maintenance mechanisms of dissociation?

Understanding the psychological mechanisms of a pathological presentation is vital to developing an effective intervention for it. Seminal work developing (now gold standard) cognitive behavioural therapy (CBT) interventions for anxiety disorders[24] and PTSD[25] have demonstrated the clinical efficacy of identifying, verifying, and then precisely targeting the underlying causal mechanisms of the problem to be treated[26]. However, much remains unknown about the psychological mechanisms underpinning dissociation. To date, only two experimental studies inferring causality in dissociation have been carried out: one of which was by our group[27,28].

In our recent work, we began the process of identifying plausible mechanisms of FSA-dissociation[4], resulting in a provisional cognitive model of the problem (Figure 1). This model suggests that dissociative experiences are maintained by a two feedback loops. The first is caused by catastrophic appraisals (negative interpretations or beliefs about the dissociative experience), which lead to rumination and counterproductive 'safety behaviours' (actions intended to mitigate potential harm), both of which serve to keep attention focused on the dissociation and reinforce interpretations of this experience as threatening. This first loop therefore proposes three possible maintenance mechanisms: catastrophic appraisals of dissociation, perseverative thinking (rumination), and counterproductive safety behaviours.

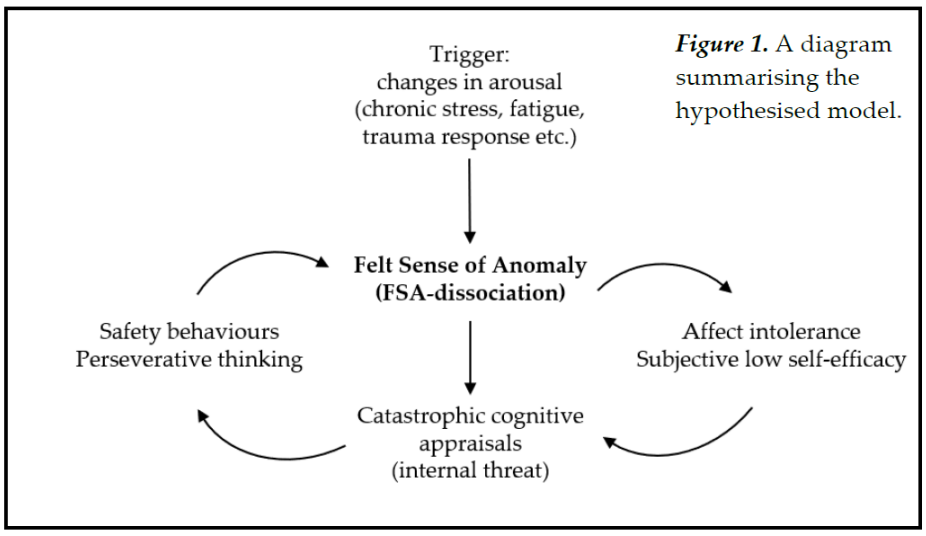

Figure 1. A diagram summarising the hypothesised model.

The second hypothesised feedback loop explains why the appraisals of dissociation are catastrophic in nature – as opposed to benign or benevolent. Across two large studies of online survey[4] and NHS patient[22] (psychosis) respondents, previous data has indicated relationships between dissociation and both high affect intolerance and low self-efficacy. In essence, people who feared shifts or peaks in their mood, and simultaneously felt powerless to manage or cope with challenges, were more likely to have FSA-dissociative experiences – as was indicated by previous qualitative evidence[6]. This second feedback loop therefore suggests two further plausible mechanisms of dissociation: affect intolerance and self-efficacy.

In this project, we have chosen to focus on the three mechanisms with the largest effect sizes from this research: negative cognitive appraisals of the dissociative experience (causal effect 0.73 in a non-clinical group[4]; 0.72 in a psychosis group[22]), perseverative thinking (rumination) (0.31[4]; 0.52[22]), and affect intolerance (0.26[4]; 0.41[22]).

The current study

The aim of this project is therefore to test the three largest psychological contributors to FSA-dissociation as identified in this previous research: cognitive appraisals, rumination, and affect intolerance. Whilst there is evidence that these are all associated with dissociative experiences in the context of psychosis, to date there has been no experimental manipulation of these factors to demonstrate their role in maintaining dissociative difficulties. Evidence of their causal effect on dissociation is required before a translational psychological intervention can be developed.

Using an interventionist-causal approach (experimentally manipulating the factor of interest via attempting to ameliorate it with therapeutic techniques) allows researchers to combine an experimental test of causal relationships with the first stages of treatment development. This project constitutes an intermediate stage along the trajectory of treatment development, in that the primary aim of these three studies will be to demonstrate proof-of-concept for the interventions, in order that a larger study with adequate statistical power to test for causal relationships and treatment efficacy may be carried out.

5. OBJECTIVES AND OUTCOME MEASURES

The primary objective is to determine whether there is sufficient reason to believe that each psychological intervention targets (reduces) the psychological maintenance mechanism (factor) of interest in that study to justify running a larger study. For Study 1 the mechanism of interest will be negative cognitive appraisals of the dissociative experiences; in Study 2, perseverative negative thinking (rumination); and in Study 3, affect intolerance (aversion to the experience of one's own emotions). Therefore, the key outcomes will be measures of these three psychological factors: cognitive appraisals of dissociation, perseverative thinking, and affect intolerance.

Of relevance to future treatment development for dissociation, the secondary objective of this project is to gain a preliminary indication of the effect targeting the above mechanisms has on levels of dissociation – i.e. whether this relationship is causal. There will not be adequate statistical power in these studies to definitively answer this research question. However, data from this study may aid future research by providing initial estimates for sample size calculations.

Since we are interested in further testing and developing the techniques in this project (if this is justified by the data), we will also ask participants for qualitative feedback about their experiences of the intervention and research processes at the end of their participation, and use the experience of running this study to inform which patient-facing logs, worksheets, and diaries may be most useful in developing a future intervention.

These objectives and outcomes are summarised below:

	Objectives	Outcome Measures	Timepoint(s)
Primary	To determine whether the psychological intervention is likely to reduce the psychological maintenance mechanism (factor) of interest (i.e. cognitive appraisals [study 1]; perseverative thinking [study 2]; affect intolerance [study 3]).	Study 1: CAD-P Study 2: PTQ Study 3: AIS	VAS rating: daily (throughout baseline and intervention window), or every other day (throughout follow-up window). Full measure rating: baseline, post-intervention, one month follow-up.
Secondary	To gain a preliminary indication of whether the relationship between the proposed psychological factor (cognitive appraisals; perseverative thinking; affect intolerance) and 'felt sense of anomaly'-type dissociation may be causal.	As above + ČEFSA-14	As above.
Qualitative	To improve the therapy intervention and research processes for use in future treatment development studies.	Qualitative feedback from participants. Audit of which patient-facing therapeutic materials were used.	At one-month follow-up (end of participation).

6. STUDY DESIGN

This project consists of three randomised multiple baseline design (MBD) single case experimental design studies, with an $A_1B_1A_2$ structure (Appendix A).

Each study will have four participants. After completing a baseline assessment, each will be randomised to a different length of baseline (phase A_1) duration (either 1, 2, 3 or 4 weeks). During A_1, participants will rate the target maintenance mechanism (factor) and their level of dissociation daily (see Section 9.6, *Assessments*).

The treatment window (phase B_1) for each participant in all studies will be five weeks. In this time, participants will have four 1:1 one-hour long psychological therapy sessions with a qualified clinical psychologist who will deliver the study intervention (see Section 10, *Study Interventions*). Between-session tasks will be set as part of this intervention, to be completed by the participant alone, or with telephone or additional in-person support from the research team. Participants will continue to rate the maintenance mechanism factor and their dissociation every other day. At the end of the intervention window (phase B_1), participants will repeat the baseline assessment measures in a 'post-intervention' assessment.

The follow-up phase – phase A_2 – will last for one month following the closure of the intervention window (phase B_1). In this phase, participants will continue to make ratings of the maintenance mechanism factor and their dissociation every other day. At the end of phase A_2, participants will complete the baseline assessment measures again in a 'follow-up' assessment, and will be offered the chance to provide unstructured qualitative feedback about the research processes and intervention.

This project will be registered with ClinicalTrials.gov.

7. PARTICIPANT IDENTIFICATION

7.1. Participants

The target population is people attending NHS mental health services for an Axis I mental health difficulty who are also experiencing high levels of dissociation. Evidence indicates that such experiences are common across mental health diagnoses[14].

7.2. Inclusion Criteria

- Aged between 16 years to 80 years;
- Outpatient of mental health services (at the time of referral to the study);
- Have undergone assessment for psychological therapy in the NHS and subsequently have been entered onto a waiting list for said therapy;
- Experiencing significant levels of 'felt sense of anomaly'-type dissociation (defined as a score within the 'moderate severe' or 'severe' range on the ČEFSA-14 (i.e,, score of 39 or above); *Černis et al., in prep.*);
- Want help to improve their dissociative experiences;
- Willing and able to give consent for participation in the study;

- Available to undertake the baseline assessment in the indicated week;
- Available to undertake the therapy sessions within the indicated therapy 'window'.

7.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Diagnosis of an Axis II ("personality") disorder;
- Primary diagnosis of alcohol/substance dependency, organic syndrome, or learning disability;
- Presence of risk issues that would be a clinical priority above managing dissociative symptoms (e.g., moderate to severe self-harm; active suicidal behaviour; etc.);
- Current engagement in any other individual psychological therapy (or psychological therapy due to begin within the participation window for this study).

- A participant may also not enter the study if there is another factor (i.e., with higher clinical priority), which, in the judgement of the investigator, would preclude the participant from providing informed consent or from safely engaging with the study procedures. Reason for exclusion will be recorded in line with CONSORT 2010 Statement[29].

8. STUDY PROCEDURES

The study flow chart is shown in Appendix A, and a schedule of procedures is summarised in Appendix B.

After screening and consent, participants will have seven study visits: three assessments, and four therapy sessions.

All participants will complete three assessment visits with a research assistant. The first is at baseline (0 weeks). The second, 'post-intervention' assessment, will occur as soon as practicable after the five-week intervention window has closed (i.e., within the next working week). The exact timescale for the second assessment will therefore vary, since each participant will be randomly allocated to wait either one, two, three, or four weeks between the baseline (0 weeks) assessment and the start of the intervention (see diagram below). All 'follow-up' assessments will take place one-month after the participant's post-intervention assessment. Additionally, all participants will complete a brief (two-item) survey via telephone, text message, or online survey (via Qualtrics) daily throughout the pre-intervention phase, and every other day during the intervention and follow-up phases; see Section 9.6 '*Assessments*'.

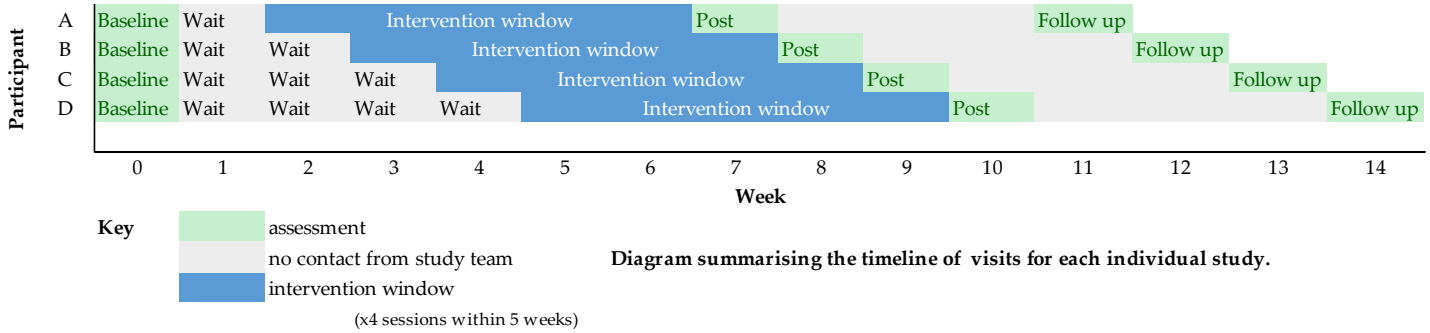

Diagram summarising the timeline of visits for each individual study.

All participants will receive the intervention for that study (i.e., targeting cognitive appraisals [study 1]; perseverative thinking [study 2]; or affect intolerance [study 3]). Four 1:1 therapy sessions will take place within the five-week intervention window. This allows some flexibility for therapist and participant in the case of absence, illness, or other difficulty scheduling appointments. More detail is given in Section 10, '*Study Interventions'*.

We will inform participants' relevant clinical team that they are taking part in the study (e.g., via the clinical notes system, or feedback to the referring clinician).

8.1. Recruitment

The recruitment target is 12 participants (four participants in three studies). Recruitment will be conducted in two local NHS mental health trusts: Birmingham Women's and Children's NHS Foundation Trust, and Birmingham and Solihull NHS Foundation Trust. Participants will be recruited from the NHS services accessible to help-seeking people aged 16 and over that hold psychological therapy waiting lists. The services include specialist early intervention in psychosis services (EIP: ages over 14 years), and adult mental health teams (AMHTs), as well as Psychological Services. Support for the project has been established with the relevant clinical leads; notably within the early intervention in psychosis service (Forward Thinking Birmingham), and with the Lead for Psychological Therapies.

The principal method of recruitment will be from routine clinical services. The clinical team or clinical research network (CRN) staff will identify potential referrals from the psychology waiting list and provide potential participants with the participant information sheet (PIS). Additionally, the lead researcher for this study works within clinical services one day a week, and may therefore also identify referrals and approach patients as part of their clinical role. If participants confirm they are happy to be contacted by the research team their contact information will be passed on the research team for this purpose. The research team will make a note of the verbal consent in their contact records. If participants do not want their contact details passed on to researchers at this time, they may retain the PIS and contact the researchers themselves at a later stage.

In a previous study with similar recruitment methods, the Lived Experience Advisory Panel (LEAP) for that trial emphasised the importance of patients also self-initiating referral to the study, in order to minimise the chances that particular patients are overlooked by clinical teams or the clinician was not present at a referral meeting. Therefore, we will also advertise the study (including via social media, online, posters present in NHS buildings, and other relevant sites). Hence, patients will be able to self-refer to take part in the study. However, in all instances we will also seek to confirm that a member of their clinical team gives approval for a patient to enter the study.

8.2. Screening and Eligibility Assessment

The eligibility assessment will be conducted by a research assistant under the supervision of a qualified clinical psychologist. The screening will take place at either an NHS clinical base, University clinical research site, or the patient's home, depending on their preference.

The eligibility assessment will include confirmation of the key clinical problem and availability for participation including:

- Self-report questionnaire assessing dissociation (ČEFSA-14; Černis et al., *in prep.* – based on the original ČEFSA[21]);

- Confirming that the patient meets inclusion and exclusion criteria – particularly clinical assessment / confirmation of the clinical team's assessment that there are no imminent risk issues that would take clinical priority for treatment (see section 8.3 '*Exclusion Criteria*');

- Checking that the patient is available to participate according to the anticipated schedule of the study: i.e., that they would be able to undertake the baseline in the designated week, would be willing to commit to four sessions of therapy, are not anticipating extended absences during the weeks in which the intervention window may fall, and will not be commencing any psychological therapies within the study participation period.

The above discussion and completion of the ČEFSA questionnaire will take place under informal verbal consent of the patient and implied consent through completion of the questionnaires on the understanding that the purpose of these activities are to determine the applicability of the research to the patient, thus minimising the risk of them beginning a burdensome research assessment under formal written consent only to discover that the study is irrelevant to them. The patient will be made aware that any discussion notes or questionnaire forms completed during the eligibility assessment will be securely destroyed once (in)eligibility has been determined and their contact details will be deleted at the end of the study.

8.3. Informed Consent

Written informed consent will be obtained by either the research worker (who will be sufficiently trained for this purpose) or a qualified clinical psychologist from the research team. This will be after the clinical team approval to approach the patient, provision of the participant information sheet to the patients, opportunities to ask questions and at least 24 hours to decide.

Written or electronic versions of the Participant Information Sheet (PIS) and Informed Consent Form (ICF) will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, 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, or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the ICF. If completed electronically, typed signatures will suffice. Copies of the consent form will be retained in the researcher site file, provided to the participant, and uploaded to the participants' electronic medical records.

Young people aged 16-18 years can be considered competent to consent to research and therefore, no parental consent to participate in the project will be sought. A qualified clinical psychologist trained in assessing capacity will assess the potential participant's competence to consent to research if they are aged 16 or 17 years. If aged 18 years or above, capacity to consent will be assessed by a GCP-trained research assistant, with further assessment by the clinical psychologist in cases where capacity is unclear.

8.4. Randomisation

Randomisation will be carried out by a researcher outside of the study team. They will randomly allocate a baseline phase duration (one, two, three, or four weeks[30]) to a letter (A, B, C or D). This will be repeated for each of the three studies. Allocations will be recorded via the use of sealed envelopes, which will be stored securely by the CI. At each baseline assessment appointment, after the measures have been completed, the research assistant will select envelope A for the first participant, B for the second, and so on, and open the envelope to reveal to the participant how long their randomly-

allocated baseline phase will be. This will then be recorded in the baseline CRF and communicated to the therapist.

8.5. Blinding and code-breaking

This study does not involve blinding. However, to incorporate a degree of impartiality, assessments will be carried out by a research assistant, not the therapist.

8.6. Assessments

All participants will undertake the baseline assessment in the same week, following a concurrent randomised multiple-baseline study design. Participants will undertake three assessment visits with the research assistant (these are referred to in SCED terminology as 'standard' assessments), and frequent ratings of the two primary constructs between assessments, throughout the course of the study (these are referred to as 'target' assessments)[31]. All assessments will use a study ID in place of identifying information.

9.6.1 'Standard' Assessments

The baseline, post-intervention, and follow-up assessments will each last approximately 50 minutes. The assessment will be conducted at an NHS or University of Birmingham building, or the participant's home, based on participant preference. The assessment will be conducted on an individual basis, with only the participant and researcher present. Assessments can be conducted remotely (for example using telephone, online, or postal versions) if necessary. Online assessments may be in the form of either: the participant annotating an electronic (Word document) version of the measures; the RA annotating a hardcopy or electronic copy of the measures whilst on a call with the participant; or via Qualtrics. Self-addressed stamped envelopes will be provided for participants returning measures by post, in the case that it is not practicable for the RA to collect these in person to ensure safe receipt.

All assessments in the study are self-report measures; except for the recording of the participant's clinical diagnosis and current prescribed medication, which will be extracted from their clinical records at each assessment point. Permission to access clinical records for this purpose will be obtained during the informed consent process.

The self-report outcomes collected at <u>all</u> three standard assessments are:

1. 'Felt sense of anomaly' (FSA)-type dissociative symptoms:

- Černis Felt Sense of Anomaly scale – revised (ČEFSA-14; Černis et al., *in prep.* – based on the original ČEFSA[21])
- Visual analogue scale (VAS) rating 0-100 for FSA-dissociation.

2. Possible mechanisms of FSA-type dissociation:

- Cognitive Appraisals of Dissociation in Psychosis scale (CAD-P[2]);
- Perseverative Thinking Questionnaire (PTQ[5]);
- Affect Intolerance Scale (AIS[1]);
- Online Alexithymia Scale (amended) (OAS[4]);
- General Self Efficacy scale (GSE[3]);
- Responses to Dissociation scale (RTD[4]).
- VAS rating (0-100) for the study-specific mechanism of interest (i.e., cognitive appraisals [study 1]; perseverative thinking [study 2]; affect intolerance [study 3]).

3. Self-harm:

- One item asking the frequency of recent self-harming behaviours. A full validated measure of self-harm and suicidality is not included as this study is not powered to establish clinical effect, but nevertheless, this rough indicator will provide helpful insight for future studies as it has been suggested that self-harm may also act as a mechanism or trigger for dissociative experiences[8].

Additionally, at the baseline assessment (only), basic demographics (age, gender, ethnicity) will be collected, and a brief summary of the participant's previous experience receiving psychological therapy.

9.6.2 'Target' Assessments

Between standard assessments, participants will be asked to complete two visual analogue scales (VAS) either daily (during the baseline (A_1) phase), or every other day (during the intervention (B_1) and follow-up (A_2) phases). These will ask the participant to rate from 0 to 100: 1) the severity of the distress caused by dissociation since the last rating, and 2) how much they have been bothered by the study-specific psychological factor (i.e., cognitive appraisals [study 1]; perseverative thinking [study 2]; affect intolerance [study 3]) since the last rating.

To help participants remember to complete these measures, and to reduce participant burden, participants will decide with the research assistant the most convenient way for them to complete the scales (e.g. via telephone call, text message, completion of an online survey link sent via email or text, or taking home a supply of paper copies), and how they would like the researcher to remind them to complete these (e.g., a daily text, automated emails, or a call once a week). Responses received via text will be transferred and stored on UoB servers as per UoB IT guidance.

9.6.3 Qualitative Feedback

At the end of the follow-up assessment (only), participants will be given the opportunity to provide qualitative feedback regarding the study procedures and therapy. This is voluntary. If a participant does choose to give feedback, they will be given the option of providing written or audio-recorded feedback (consent for audio recording capture, storage, and transcription will be covered in the ICF for the study) in the follow-up assessment appointment.

Additionally, all participants will be given a link to an anonymous online 'comments box' (online survey text box on Qualtrics) in case they wish to give feedback after the appointment, or do not feel comfortable giving feedback to the research assistant directly.

The feedback will take an unstructured form, with no topic guide or interview schedule – except that participants will be prompted to provide feedback on 'how you found both the study process, and how you found the therapy', and that 'we are interested in negative feedback as well as positive, so that we can learn how to improve the experience for future participants'.

If feedback is given verbally, it will be audio-recorded and transcribed verbatim. All feedback will be analysed using Thematic Analysis[32]. Quality guidelines[33] will be followed, including credibility checks and reflexive practice. This approach has been used before by the CI with a similar participant group[6].

8.7. Early Discontinuation/Withdrawal of Participants

During the course of the study, a participant may choose to withdraw early from the study at any time. This may happen for several reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE.
- Inability to comply with study procedures
- Participant decision

Participants may choose to stop treatment and/or study assessments but may remain on study follow-up. Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely. Withdrawal from the study or intervention will not affect their usual care.

According to the design of the study, participants may have the following two options for withdrawal;

1) Participants may withdraw from active follow-up and further communication but permit data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data would be collected after withdrawal.

2) Participants can withdraw completely from the study and withdraw the data collected up until the point of withdrawal. The data already collected would not be used in the final study analysis, unless analysis has already begun/been completed.

In addition, the Investigator may discontinue a participant from the intervention 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 which requires discontinuation of the intervention;
- Clinical decision.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

The reason for withdrawal will be recorded in the CRF.

8.8. Definition of End of Trial

The end of study is the date of the last study contact.

9. STUDY INTERVENTIONS

In each of the three studies, participants will be offered four one-hour sessions of individual therapy with a qualified clinical psychologist with expertise in dissociative difficulties. These will take place within the five-week intervention window, and will be held at an NHS or University of Birmingham site, or the participant's home, according to their preference.

Each intervention will target the putative maintenance mechanism of interest for that study (see below). In each study, the first session will also include socialisation to the therapy session format and psychoeducation about how the mechanism might relate to dissociative experiences. Sessions 1 to 3 will involve learning and practicing active change techniques, whilst the final session will focus on consolidation of new information, planning for the future, and managing the therapeutic ending.

Practice of techniques between sessions will be encouraged, and may be supported by additional between-session contact (e.g. text messages, telephone calls, or meetings to carry out behavioural experiments in a supported manner) with an assistant (graduate-level) psychologist where indicated.

This therapy will be provided in addition to usual care. The quality of the therapy will be checked by the independent rating of audio-recordings of sessions by the therapist's clinical supervisor. Audio-recording of therapy sessions is optional – permission will be sought from participants at each session, and verbal consent confirmed at the start of the recording. Each time, participants will be reminded that they may request the recording to stop and/or be deleted at any time. To enable reporting of treatment delivery and fidelity, details such as the date, duration, and key discussion topics of each session will be recorded by the therapist for each session. All missed or cancelled therapy appointments will be recorded.

As noted above (6. Objectives And Outcome Measures), one of the aims of the study is to understand which therapy materials may be most helpful for future treatment development. Therefore, the details below – particularly with respect to administration of patient-facing materials – are preliminary and subject to personalisation for each participant as appropriate. Full details of this personalisation will be recorded and reported.

9.1. Study 1 – Negative Cognitive Appraisals of Dissociative Experiences

The key therapeutic technique delivered in this intervention will be cognitive restructuring, drawn from classical cognitive-behavioural therapy (e.g.[34]).

Participants will be supported to understand what cognitive appraisals are, learn to notice and record these using a cognitive appraisals log/diary, and then supported to use an extended log/diary to challenge and adjust any negative assumptions contained within these. The aim is for participants to become more aware of the automatic appraisals they are making of their dissociative experiences and replace these with more balanced judgements.

There is extensive evidence for the use of this technique across the full range of mental health presentations, particularly in depression and anxiety, but also in a dissociative diagnosis: depersonalisation disorder[35].

9.2. Study 2 – Perseverative Thinking (Rumination)

The key therapeutic techniques delivered in this intervention will be those used effectively in a four-session worry intervention for persecutory delusions[36].

Participants will be supported to consider their positive and negative beliefs about worry, identify their typical triggers for worry, and learn and practice problem-solving and worry-management techniques.

This therapy has been thoroughly tested in the context of psychosis[36–38] and demonstrated to be effective in reducing worry, as well as the downstream effect of worry in this context: paranoia. It is therefore anticipated to have a similar effect in the context of dissociation.

9.3. Study 3 – Affect (Emotion) Intolerance

The key therapeutic techniques delivered in this study will be drawn from CBT and dialectical behavioural therapy (DBT).

Participants will be supported to explore their own beliefs about emotions (CBT) and learn why affect is necessary and adaptive for daily life (DBT). They will work with the therapist to identify their individual triggers for affect intolerance (CBT/DBT) and respond to these in the most relevant way, including: learning and practicing DBT coping strategies; carrying out behaviour experiments to test their assumptions/beliefs (CBT); or carrying out cognitive restructuring to balance beliefs/appraisals (using the same techniques as in Section 10.1, *Study 1*; CBT).

These techniques have been used effectively in the treatment of emotion dysregulation and affect intolerance[39]. They are therefore anticipated to have a similar effect in the context of dissociation.

10. SAFETY REPORTING

Adverse events are rare in these kinds of studies. Adverse events are likely to come to the attention of the assessor or therapist, but all medical notes will be systematically checked for serious adverse events following completion of the final assessment to ensure all adverse events are recorded. The responsible clinical team will be informed of any adverse event. The responses to an adverse event will be determined on a case-by-case basis. The University of Birmingham Quality Management System procedures for safety reporting will be followed.

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Formal complaints regarding therapy or research procedures will also be recorded.

10.2. Reporting Procedures for Serious Adverse Events

All serious adverse events that come to our attention are reviewed by the study team. These include serious events which are:

- Related to the intervention/study procedure related or not;
- Anticipated and unanticipated serious events;

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

The study team will make an initial assessment of whether the SAE is potentially related to the study procedures or intervention and report to the regulatory authorities within the appropriate timescales.

10.3. Events exempt from immediate reporting as SAEs

Hospitalisation for a pre-existing physical health condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute a serious adverse event.

11. DATA ANALYSIS

The statistical aspects of the project are summarised here, and will follow the procedures recommended for this study design[40].

11.1. Statistical Analysis

Given the design and sample size, analysis will be descriptive in nature and no hypothesis testing will be carried out. The three studies will be analysed separately according to the following analysis plan.

12.1.1 Quantitative data

First, patient outcome measures will be presented graphically, and visual and statistical analysis used to assess within- and between-phase data patterns, as per the recommendations for SCEDs[40].

- Within-phase analysis:
    - level (mean and standard deviation and/or median and interquartile range);
    - trend (visual analysis or whether datapoints are increasing / decreasing);
    - stability (whether 80-90% of datapoints fall within 15% of the mean or median[40]).

- Between-phase analysis:
    - Immediacy of effect (visual analysis);
    - Consistency of data patterns (visual analysis; trend analysis);
    - Overlap between phases (nonoverlap statistics e.g. extended celeration line or two standard deviation band method; as appropriate[40]).

The above information will be used to form a judgement as to whether the data indicates that the intervention is causing a change in outcome measure scores. If so, effect sizes (Tau-U[41]) will be calculated.

12.1.2 Qualitative data

Written and transcribed qualitative data arising from requests for feedback on the research process and therapy intervention (see Section 9.6.3, *Qualitative Feedback*) will be analysed using Thematic Analysis[32]. This analysis will be managed within qualitative analysis software. Quality guidelines[33] will be followed, including credibility checks and reflexive practice. This approach has been used before by the CI with a similar participant group[6]. Key themes arising from this analysis will be reported within the study results.

11.2.Sample Size Determination

The aim of SCED studies is to use repeated phases with and without the application of the experimental intervention to demonstrate that it is the intervention that is causing the observed effect.

In essence, this allows the same participant to contribute both control and intervention data, increasing information about probable cause and effect in contexts where it may not be feasible to run a fully powered randomised controlled trial[31]. General convention suggests that demonstrating changes in the outcome measure after introducing or withdrawing the intervention must be done a minimum of four times to imply a functional relationship between intervention and effect[40]. Typically, this can be achieved by repeatedly introducing and withdrawing an intervention with the same participant. However, this method is less valid in clinical psychology, where carry-over effects are expected from the intervention, and repeating the intervention may not be practicable. Thus, the multiple-baseline design (MBD) across individuals allows the requisite number of transitions (from intervention to 'no intervention' and vice versa) to be achieved, whilst each participant only undergoes the treatment once. Randomising the length of the baseline phase for each participant means that any observed effect cannot be better understood as a function of time elapsed since the baseline assessment or other research procedure. The minimum number of participants required for an MBD study is two, although three or more is typical[42]. Thus, this project will use a sample size of four participants per study, to mitigate against any potential drop out or high levels of missing data.

11.3. Analysis Populations

All participants recruited to the study will be documented fully with respect to receiving the intervention and participating in follow up. Adverse events will be reported for all participants.

11.4. Decision points and stopping rules

There are no interim analyses or formal stopping rules in relation to this study given the small sample size and its exploratory nature.

11.5. The Level of Statistical Significance

This is not applicable: no significance testing will be undertaken given the small sample size and exploratory nature of the study.

11.6. Procedure for Accounting for Missing, Unused, and Spurious Data.

There will be no statistical methods applied for handling missing data as this approach is inconsistent with the single experimental case design. For each participant, phases with fewer than five datapoints will be omitted from analysis, since this is the minimum recommended for within-phase analyses[40].

12. DATA MANAGEMENT

The plan for the data management of the study is outlined below. There is not a separate Data Management document in use.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which current diagnosis and medication levels may be extracted to record in the CRF), and study assessment measures.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by a participant number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections.

12.3. Data Recording and Record Keeping

All study data will be entered on paper or electronic CRFs and transcribed or entered directly to the clinical data management system. Data will be anonymised using a unique study ID. Personal data and participant identification codes will be kept separately from the research data. Access to these data will be strictly on a need-to-know basis. Any secure data transfer will take place in accordance with University of Birmingham policies.

Data will be entered from paper CRFs to the clinical database, or recorded directly on eCRFs as soon as possible after the study visit. Validation of all data entered into the clinical database is achieved through manual review. All critical data items are 100% checked against original source documents, where applicable, to ensure accuracy and an error rate is established across all fields to ensure a consistently accurate dataset.

Audio recordings of therapy sessions and feedback will be taken using a password-protected recording device. They will be immediately deleted from the device once they are transferred onto a secure university server. Recordings should be transferred and deleted from the device within one working day of the appointment in which they were made.

Recordings of therapy sessions will be used for the purposes of clinical supervision and treatment development only. These will be downloaded, encrypted, and stored on a secure server. Only a qualified clinical psychologist will have access to this data for the sole purpose of ensuring the quality of the therapy. All audio-recordings will be deleted one year after the end of the study.

Recordings of qualitative feedback will be transcribed by the research team. Transcriptions will be de-identified, and audio files will be deleted after the transcripts have been checked for accuracy by a second researcher. Transcripts will be used along with written qualitative feedback as outlined in section 12, '*Data Analysis*'.

Electronic data will be kept on a secure University of Birmingham server. Hard copy of data will be kept in a locked filing cabinet in a locked University of Birmingham office.

The report of the study will not identify any individuals. Data will be kept for 10 years following publication of the results.

13. QUALITY ASSURANCE PROCEDURES

13.1. Risk assessment and monitoring

The study will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. Data will be evaluated for compliance with the protocol, standard operating procedures, GCP, and accuracy in relation to source documents. All electronic data entry is double checked against the source documents.

13.2. Trial committees

Given the small size of the project, there will be no trial steering committee or Data Monitoring and Ethics Committee. Instead, the functions of a trial management group will be performed by the CI, who has extensive clinical trials experience.

14. PROTOCOL DEVIATIONS

A trial related deviation is a departure from the ethically approved study protocol or other study document or process (e.g., consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

15. SERIOUS BREACHES

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial".

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, regulatory authority, and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

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

16.3. Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

Both substantial and non-substantial amendments will be submitted to the sponsor for review and approval prior to submission to the relevant regulatory authorities.

16.4. Other Ethical Considerations

We anticipate few ethical concerns for patients entering this study. The study will be conducted by a CI who is a qualified clinical psychologist with extensive experience of clinical trials, and who has appropriate training regarding the management of any risk or safeguarding issues that may arise during the course of the study. There is a risk that safeguarding concerns are raised (e.g. identification of risk of self-harm etc.). These will be reported as soon as possible to the direct care team, and the participant supported appropriately within the boundaries of the trial (e.g. signposted to Samaritans, reminded of existing risk-management plan, etc.)."Participation in the study does not change existing treatment receipt, so there is no disadvantage in taking part. Participants will be free to discontinue the study at any point, without needing to give an explanation.

The main potential problem is the burden of assessments (three visits and daily/alternate-day reporting for two key items); however, most trials with similar patient groups show a modest symptom benefit of entering the control condition in a therapy trial, most likely due to the additional monitoring and sensitive manner of the research assessors (e.g.[43]). We offer payment for participants' time and flexibility in the assessments, such as providing breaks, or arranging for these to take place at a location of participants' choice – including online. The study questionnaires ask participants about their mental health, which may be considered a sensitive topic. However, these are issues participants are already managing outside of the study, and they will have experience of talking about them as part of the treatment they are receiving from NHS services. Research assistants are trained to ask questions sensitively and participants are informed that they do not have to answer any questions if they do not want to.

The therapy consists of techniques that have been delivered previously in clinical practice and research trials without adverse events in other clinical groups. Although the techniques have not yet been applied to a high dissociation group, the CI's clinical practice has given no indication that the techniques would be inappropriate for this specific group, nor are they expected to cause any undue upset or distress beyond that which could be expected in psychological therapy. During the intervention, participants will be invited to consider alternative actions and patterns of thinking to assist them in overcoming their difficulties. The pace of therapy is dictated by the participant and the intervention is a collaboration between the therapist and the patient.

Safety of researchers is very important; therefore, we follow the NHS Trust's standard operating procedure for lone working.

16.5. Reporting

The CI shall submit a Progress Report to the REC,, host organisation, funder, and/or Sponsor on an annual basis. In addition, an End of Trial notification and final report will be submitted to the same parties.

16.6. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic databases. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.7. Expenses and Benefits

Reimbursement of participants, including payment for their time at research assessments and travel, are calculated following guidance from the McPin Foundation and INVOLVE guidelines.

Participants will be compensated £15 for their time for each research assessment in the study (a total of £45). Additionally, for each of the three phases (baseline/A_1, intervention/B_1, follow-up/A_2), participants will be offered a further £15 if they complete five or more VAS ratings in that phase. Therefore, participants may be compensated a maximum total of £90 across the study.

Reasonable travel expenses for any visits additional to normal care (including parking costs) will be reimbursed on production of receipts, or a mileage allowance provided as appropriate. Where receipts are not readily available, for example parking fees, the requirement to provide these before payment will be waived.

17. FINANCE AND INSURANCE

17.1.Funding

The study is funded by a research allowance allocated to Dr Emma Černis by the School of Psychology, University of Birmingham.

17.2. Insurance

The University has in force a Public Liability Policy and/or Clinical Trials policy which provides cover for claims for "negligent harm" and the activities here are included within that coverage.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with any third parties involved in the project.

18. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. The role of the funder will be acknowledged in all publications. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. All participants will be offered a copy of the results. Specific consent to use de-identified participant quotes will be sought prior to publication. Reporting of the study will follow the Single-Case Reporting Guideline In Behavioural Interventions (SCRIBE) recommendations[44].

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The protection and exploitation of any new IP is managed by the University's technology transfer office.

20. ARCHIVING

Archiving will be completed after publication of the study outcomes. Data will be stored securely at the University of Birmingham for 10 years post publication.

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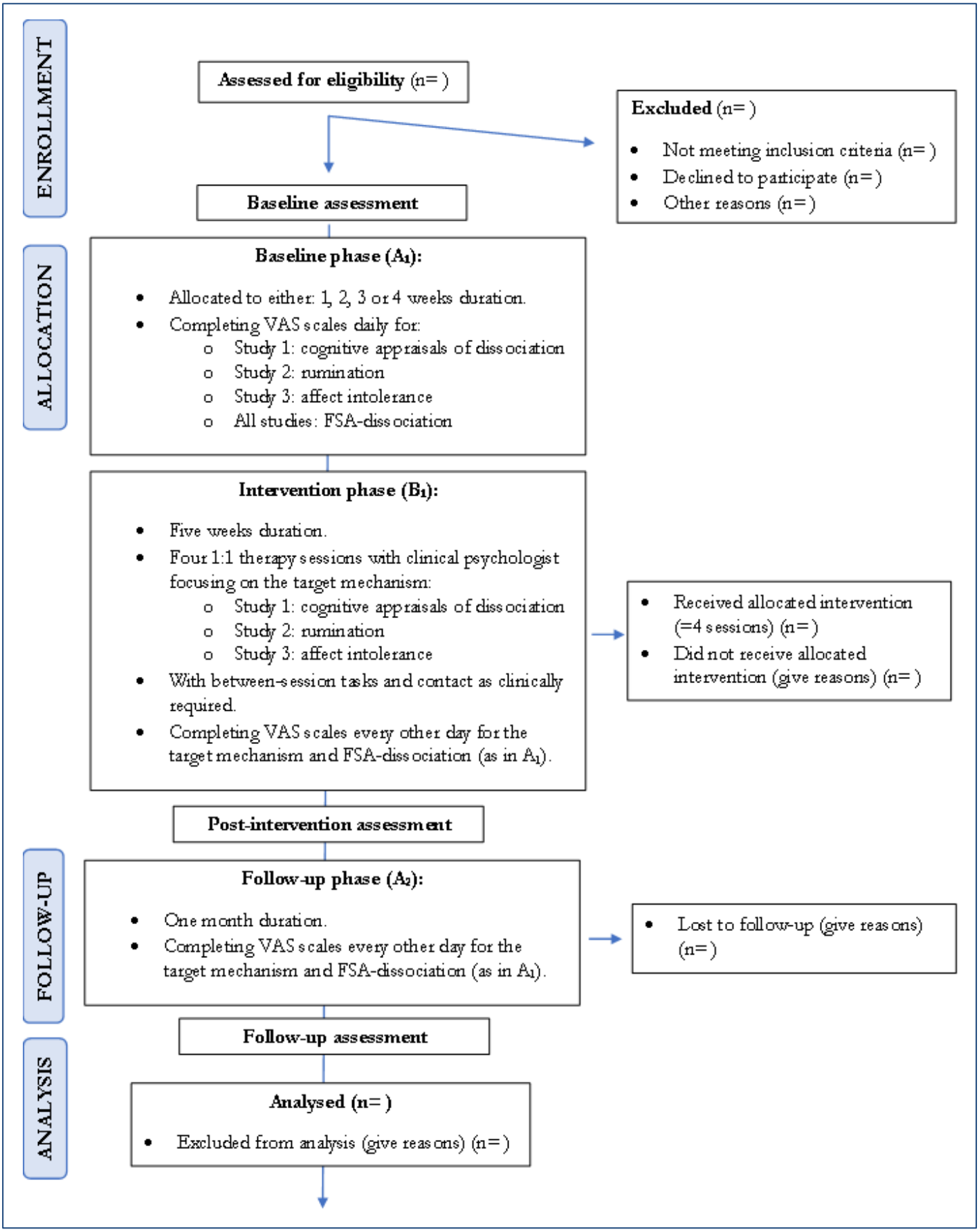
22. APPENDIX A: STUDY FLOW CHART



23. APPENDIX B: SCHEDULE OF PROCEDURES

Procedures	Screening	Baseline (0 weeks) assessment	Baseline phase (A_1) (1, 2, 3 or 4 weeks)	Intervention window (B_1) (5 weeks)	Post-therapy Assessment	Follow-up phase (A_2) (1 month)	Follow-up Assessment
Study procedures							
Eligibility assessment	X						
Informed consent		X					
Randomisation		X					
Adverse event monitoring	X	X	X	X	X	X	X
Data collection							
Demographics		X					
Diagnosis and medication (from clinical records)		X			X		X
Measure of FSA-dissociation (*CEFSA-14)*		X			X		X
Measures of feasible maintenance mechanisms (*CAD-P; PTQ; AIS; OAS; GSE; RTD*)		X			X		X
Self-harm		X			X		X
VAS scales (dissociation; study-specific mechanism)		X	X*	X**	X	X**	X
Qualitative feedback regarding therapy and study							X
Interventions							
NHS treatment as usual	X	X	X	X	X	X	X
Study intervention (4 sessions)				X			

Key: * = daily; ** = every other day

24. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
NSA01	1.2	31-08-2023	Emma Černis	Amended pre-registration location from ISRCTN to ClinicalTrials.gov
NSA02	2.0	07-09-2023	Emma Černis	Amended entry criterion for ČEFSA-14 scale to include 'moderately severe' as well as 'severe', and clarified that this corresponds to a score of 39 or more.

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee, HRA (where required) or MHRA.