# Statistical analysis plan (SAP) and study protocol

**Official title:** Implementation and Evaluation of Prolonged Exposure Psychotherapy for Adverse Events in Early Phase Psychosis with Comorbid Substance Misuse

**Brief title:** Psychotherapy for psychosis, adverse events, and substance misuse

**NCT#**04546178


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## Acronyms

| | |
|---|---|
| AE(s) | Adverse event(s) |
| SM | Substance misuse |
| EPP | Early phase psychosis |
| PE | Prolonged Exposure therapy |
| PE+ | Adapted Prolonged Exposure therapy |
| NSEPP | Nova Scotia Early Psychosis Program |
| MBD | Multiple baseline design |
| RCI | Reliable change index |

**Updates**

1) June 17, 2023
    **a.** Updated the scores to include the RCI for the PCL-5 (8-item version) and WHO ASSIST – cocaine subscale
2) November 26, 2023
    **a.** Updated the WHO ASSIST subscale to include scores for Sedatives

**Background and rationale**

Research has found that adverse events (AEs) and substance misuse (SM) individually influence the onset of psychosis and its clinical outcomes (Conus et al., 2010; Lambert et al., 2005). AEs are defined as "negative events that have occurred […] and are outside the control [of the individual], and cause harm or the potential for harm along with stress" (Burgermeister, 2007); they include traumatic events (e.g., child abuse) and less severe events with a similarly negative impact (e.g., discrimination). Previous studies have estimated that 30-75% of individuals with psychosis have experienced at least one AE that predates their psychotic symptoms (Bendall et al., 2007). AEs sequelae (e.g., avoidance) are often risk and maintenance factors of psychosis and AE-related mental illnesses (e.g., depression, post-traumatic stress disorder (PTSD; Gibson et al., 2016), as well as contributing to the development of substance misuse (Khoury et al., 2010). Substance misuse (SM) is estimated to exceed 55% in individuals with psychosis (Ouellet-Plamondon et al., 2017) and leads to more negative functional and symptomatic outcomes. The psychosis proneness-persistence-impairment model (van Os et al., 2009) states that psychological mechanisms can sensitize an individual at risk, resulting in the emergence and persistence of psychotic symptoms; the stress and coping theory echoes this model for SM. Targeting these psychological mechanisms, especially those in common among psychosis, substance misuse, and AE sequelae, may reduce symptoms and associated impairment.

Avoidance and hopelessness are psychological mechanisms involved in all three conditions; they are maintenance factors of psychosis and result in greater symptom severity (Tully et al., 2017), sequelae of AEs that contribute to mental illness development and maintenance (Kleim et al., 2012), and are both risk and maintenance factors for SM (Malmberg et al., 2010). Prolonged exposure therapy (PE), a form of cognitive behavioral therapy, is an evidence-based intervention for PTSD with and without comorbid SM disorders (Mills et al., 2012). PE addresses avoidance to feared reminders of an AE through exposure (i.e., imaginal, in vivo), an effective therapeutic component, and reduces hopelessness through mastery experiences. PE has also been investigated in chronic psychosis (generally >10 years with illness). van den Berg and colleagues (2015) tested the efficacy of PE in adults with a psychotic disorder and PTSD; they compared treatment outcomes to a group treated with eye movement desensitization and reprocessing (EMDR) therapy and a waitlist-control group. The PE condition group experienced: a significant reduction in PTSD symptoms, PTSD remission, a significant reduction in paranoia and depressive symptoms, and an increase in functioning (de Bont et al., 2016). Frueh et al (2009) also studied the effect of PE in chronic psychosis and noted a reduction in PTSD symptoms and 12 of 13 participants achieved and maintained remission of their comorbid

PTSD diagnosis by 3-months post-treatment. These studies demonstrate the wide-ranging benefits that can be seen with PE therapy in individuals with long-standing psychotic disorders.

However, PE has been studied exclusively in individuals with chronic psychosis. A recent study (Jones et al., 2019) found that young adults who were in the early phase of psychosis (EPP) and had a history of AEs had the poorest treatment outcomes when the AEs were not addressed, suggesting a gap in care. Importantly, adapting and implementing PE therapy in early phase psychosis may result in more significant positive outcomes than in chronic psychosis, as young adults in EPP have not yet sustained the same degree of biological and psychological burden of a long-term psychotic illness (Lieberman et al., 2001), substance dependence, and their cognitive capacities tend to be less affected. Overall, they are able to better engage in and benefit from psychological interventions. We also know that young adults with EPP want treatment for difficulties related to AEs. Tong et al. (2017) qualitatively examined individuals in EPP who were in therapy to discuss AEs; participants reported that desire for change was a major motivating factor for them to initiate and remain in therapy and talk about their experiences. Additionally, Halpin et al. (2016) found that therapy for AEs helped foster insight into the development and maintenance of patients' EPP, which aided in their recovery. All of this suggests that treatment for AEs is needed in EPP.

However, PE does not address emotion regulation, an effective treatment strategy recommended for individuals with a psychotic disorder who have experienced adversity (Bloomfield et al., 2020), nor does it include acceptance strategies, another recommended component. Although PE therapy includes many effective therapeutic components for the treatment of AE-related symptoms, the addition of several third-wave strategies may increase its effectiveness in the treatment of AE-related symptoms.

The specific aim of this project is to address an identified treatment gap in early intervention care by combining PE therapy with emotion regulation and acceptance strategies, which we are calling PE+, and applying this intervention to a younger, EPP population with AEs and substance misuse. We plan to: 1) establish the ideal treatment duration (i.e., number of sessions) that results in clinically significant change for participants, 2) determine the effectiveness of each PE+ therapy component in EPP, and 3) establish the degree that PE+ therapy impacts the severity of psychotic symptoms, substance misuse, and overall functioning. We hypothesize that PE+ treatment will result in clinically significant reductions in 1) hopelessness and avoidance, 2) negative psychotic symptoms (e.g., anhedonia), and 3) the frequency and quantity of SU; all reductions will be maintained by 2-months post-treatment. Additionally, we expect a global improvement in functioning from pre-post PE+ therapy, maintained at 2 months.

*Plain-language summary*

Research has found that adversity (e.g., abuse) and substance use (i.e., drug and alcohol use) influence an individual with a psychotic disorder's recovery: people with psychosis have significantly higher rates of adversity and substance use than people with other mental illnesses. Currently, there are few treatment options for people living with psychosis, substance misuse, and adversity-related symptoms (e.g. anxiety, depression). This is especially true for young adults who are in the first years of a psychotic illness (i.e., early phase psychosis; EPP) who may be in the best position to

benefit from treatment. Research has demonstrated that Prolonged Exposure (PE), a psychological therapy, may be appropriate for people in EPP, although there is limited evidence regarding its adaptation from use in chronic psychosis to EPP. The aim of the proposed study is to adapt and optimize PE therapy for young adults in EPP. We aim to recruit 20 individuals from the Nova Scotia Early Psychosis Program (NSEPP) aged 19-35 who will participate in 15 sessions of adapted PE (which we call PE+); we will compare their scores before and after treatment on measures of psychotic symptoms, amount and frequency of substance use, and adversity-related problems. Our goal is to improve two qualities that may be contributing to worse outcomes: avoidance and hopelessness. These are addressed by facing feared reminders of adversity and learning new ways to think about adverse experiences and mental health problems. The application of this evidence-based intervention has the potential to create a new treatment avenue for EPP, reducing impairment and distress, and improving recovery rates.

## Hypotheses

**(H1):** PE+ treatment will result in clinically significant reductions in hopelessness and avoidance
**(H2):** PE+ treatment will result in clinically significant reductions in negative psychotic symptoms (e.g., anhedonia)
**(H3):** PE+ treatment will result in clinically significant reductions in the frequency and quantity of SM; all reductions will be maintained by 2-months post-treatment.
**(H4):** A global improvement in functioning from pre- to post-PE+ therapy will occur, with gains maintained 2 months-post treatment.

## Research Plan

This study involves adapting and optimizing PE+ therapy for adults in early phase psychosis. Participants will be asked to tell us about themselves (e.g., race, gender), participate in interviews and complete questionnaires assessing their current psychosis- and adversity-related symptoms (e.g., anxiety, depression) and substance misuse, along with avoidance and hopelessness. Participants will participate in 15 psychotherapy sessions targeting adversity-related sequelae and symptom change will be evaluated throughout their participation and as an outcome.

Specific details about each instrument is available below.

### *Adversity*

1) The Trauma and Life Events (TALE; Carr et al., 2018) checklist, a 21-item yes/no questionnaire, will tell us what adverse experiences participants have experienced and when they happened. Participants also tell us whether they experienced these negative things just once, or more than once. This questionnaire also asks the participant whether those adverse events are affecting them now in any way. The authors of this questionnaire tested it with people who have psychosis so it's appropriate to use for a study like this.

2) The 40-item Trauma Symptom Checklist (TSC-40; Elliott & Briere, 1992), asks about the frequency of mental health symptoms that a lot of people experience after living through one or more adverse events (e.g., crying, feelings of guilt, insomnia). The answers possible range from

"Never (0)" to "Often (3)." Several studies have examined the validity of this questionnaire among people with psychotic disorders and have found that it is appropriate for use with this population.

***Substance use***

1) The World Health Organization's Alcohol, Smoking, and Substance Involvement Screening Test (WHO ASSIST; WHO ASSIST Working Group, 2002), an 8-item interview, will help establish substance use frequency for both illicit and legal substances. This interview also includes questions asking about the urge to use substances, difficulties in functioning caused by substance use, and difficulties cutting down or stopping substance use. Responses are on a 5-point frequency scale that range from "Never" to "Daily or almost daily." This measure has been validated for use with individuals with psychosis (Hides et al., 2009; Humeniuk et al., 2008) and is routinely collected from patients at the NSEPP, the site of this study.

***Psychotic symptoms***

1) The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) is a semi-structured clinical interview assessing positive and negative symptoms of psychosis, as well as assessing general psychopathology (e.g., depression, anxiety). Previous research suggests that this instrument has good criterion and predictive validity and is designed for use with individuals with psychosis. This interview is frequently used with patients at the NSEPP.

***Functioning***

1) The Social and Occupational Functioning Assessment (SOFAS; Morosini et al., 2000), is a clinician-rated scale assessing current functioning in both social and occupational domains. Ratings range from "1-10 – Persistent inability to maintain minimal personal hygiene/unable to functioning without harming self or others or without considerable external support" to "91-100 – Superior functioning in a wide range of activities." This measure is frequently used with patients at the NSEPP.

2) The Clinical Global Impression – Severity and - Improvement (CGI-S & -I; Guy, 1976), are two single-item clinician-rated measures. The CGI-S asks about the severity of current illness with answers ranging from "Not assessed (0)" to "Among the most extremely ill (7)". The CGI-I asks about the degree of change from baseline and response options range from "Not assessed (0)" to "Very much worse (7). The CGI-S and -I are frequently used with patients at the NSEPP.

***Therapeutic alliance***

1) The Session Rating Scale 3 (SRS-3; Duncan et al., 2003) is a 4-item instrument designed to measure ongoing therapeutic alliance, or the working relationship between the therapist and client. Participants complete this visual scale after each therapy session; they rate their perception of their relationship with their therapist, the goals and topics discussed in session, the therapist's approach/method, and the session overall.

***Therapeutic targets***

1) The Beck Hopelessness Scale (BHS; Beck et al., 1974) is a 20-item measure assessing negative expectations about the future. Items are in a yes/no format. This measure has previously been used with first-episode psychosis patients and has strong validity and sensitivity.

2) The Brief Experiential Avoidance Questionnaire (BEAQ; Gámez et al., 2014) is a 15-item measure designed to assess experiential avoidance (i.e., avoidance of distressing thoughts, emotions, memories, and physical sensations; Hayes et al., 2011). Response options range from “Strongly disagree (1)” to “Strongly agree (6).”

**Procedure**

A multiple-baseline design (MBD; Kratochwill et al., 2010) will be used to stringently examine intervention effects; this design temporally staggers intervention start times across participants, thereby creating a control group composed of each individual’s pre-intervention scores. Randomization of start time will be used to increase internal validity and minimize bias (Kratochwill & Levin, 2010). The MBD allows a fine-grained assessment of each component of the intervention; this design can detect significant change during each phase of the intervention. An MBD is well-suited to a study focused on adaptation and optimization of a psychotherapy as it will provide insight on what components have more or less effectiveness in EPP.

All new NSEPP patients are asked whether they consent to being contacted for research purposes, with approximately 80% agreeing to be contacted. Patients who consented will be contacted via their preferred method (i.e., email, telephone) and screened with the ASSIST and TALE questionnaires over the phone (see Figure 1 for procedure details). Participants must have experienced ≥1 distressing adverse lifetime event listed on the TALE questionnaire that the participant indicates still affects them now, and one score on the ASSIST must be within the “moderate” or “high” risk range for any substance (excluding tobacco products). Additionally, all participants must be aged 19-35 years, diagnosed with a primary psychotic disorder (e.g., schizophrenia, schizoaffective) within the last 5 years. If participants are deemed eligible, a baseline assessment will be scheduled and conducted. This assessment will include three self-report instruments, the BEAQ, BHS, and TSC-40, in addition to several clinician-administered measures, such as the PANSS, which will be used to assess psychotic symptoms, and the CGI-I and -S, along with the SOFAS, which will assess illness severity, symptom change, and functioning. See Figure 1 for a visual depiction of the procedure. Demographic information related to participants’ age, gender, race, ethnicity, and sexual orientation will also be collected; these variables are critical to collect as participants from a marginalized community (e.g., LGBTQ+) may have different experiences than those who are not a part of marginalized groups.

This assessment will be followed by 1-3 brief follow-up assessments, depending on the randomization to start time (i.e., 2,3, or 4-week delay between initial interview and therapy) to establish a symptom baseline. The participant’s treatment start time, decided by randomization, will be communicated to the participant at the baseline interview. However, the fact that the participant will be randomized to a treatment start time will be communicated to the participant as a part of the consent process. The participant will also participate in an assessment prior to beginning the intervention in the event that symptoms have changed since the initial baseline assessment. The BHS, BEAQ, and TSC-40 will be administered, in addition to the completion of the SOFAS, CGI-I and -S, ASSIST, and PANSS. The intervention, a 15-session course of weekly PE+ therapy, is divided into five sets of three 90-minute sessions: 1) psychoeducation about AEs, SM, and the interplay of both with psychosis; 2) emotion regulation and acceptance strategies; 3) awareness of thoughts and work on changing thoughts about AEs and SM, 4) imaginal and in vivo exposures, and 5) review of treatment and planning for termination and maintenance. After each set of 3 sessions, current symptoms and SM will be assessed using the instruments above (i.e., BEAQ, BHS, TSC-40, ASSIST). After each session, a measure of therapeutic alliance, the Session Rating Scale (SRS;

Duncan et al., 2003) will be administered to account for fluctuations in the therapist-participant relationship on assessment scores. Psychotic symptoms will be reassessed using the PANSS after the final session of treatment has been completed. There will also be two follow-up sessions 2-months post-intervention to assess maintenance of therapeutic gains using all of the same instruments as the baseline assessment; each session will take approximately 75 minutes. Participants will also be asked for their feedback on how to further optimize PE+ therapy for use with patient with EPP in the future.

All individuals working on this study will be trained to recognize signs of emotional distress and intervene immediately. The therapist(s) administering psychotherapy in this study will remind participants that they may choose to discontinue their participation at any time. If the participant appears to become very distressed during a psychotherapy session, the therapist will provide calming strategies to the participant; however, if this is ineffective, the researcher may choose to discontinue the participant's session, or reschedule the session. Any event that involves significant participant distress will be reported to the PI (Victoria Patterson) who will then report it to the NSHA Research Ethics Board immediately as an adverse event. In the event that participants report feeling distress, they will be encouraged to speak with their NSEPP clinician and, if necessary, study staff will assist the participant with making an appointment. During the informed consent process, participants will be provided with a consent form that has contact information for agencies (e.g., Mobile Mental Health Crisis Line, etc.) who can assist with intense distress in the unlikely event that participants become upset following their participation. This information will be provided to all participants. All adverse events will be reported via an "Adverse Event Notification" form, which will be filled out and submitted to Research Services at Nova Scotia Health as soon as possible following any adverse events.

**Study objectives**

**(O1):** Establish the ideal treatment duration (i.e., number of sessions) that results in clinically significant change for participants
**(O2):** Determine the effectiveness of each component of PE+ in EPP
**(O3):** Establish the effect of PE+ therapy on the severity of psychotic symptoms, adversity-related symptoms, substance misuse, and overall functioning.

**Data analysis plan**

The goal of this intervention study is to determine the effect of PE+ therapy on psychotic symptoms, substance misuse, adversity-related illness (e.g., PTSD), and functioning. Therefore, the desired outcomes of the analyses will be the significance of symptom change and its maintenance over time.

The first hypothesis, that PE+ treatment will result in clinically significant reductions in hopelessness and avoidance, will be addressed using the Reliable Change Index (RCI; Jacobson & Truax, 1991), our chosen analysis, as inferential statistics are not appropriate. A power analysis is not possible to compute given that inferential statistics are not appropriate for RCIs; however 20 participants is typical for studies using the MBD and this number is on par with previously published studies using this design (Frueh et al., 2009). The RCI criteria we will use to determine clinically significant change is that the participants' mean post-intervention assessment scores will be between the scores of a healthy population and a mentally ill population (see Figure 2; change criteria c). This criterion is neither liberal nor conservative and is the most realistic criteria given the multitude of psychological symptoms that we are aiming to treat. We will calculate the numerical criteria needed to

assess this change using previously published means and standard deviations of the measures we are using (e.g., PANSS, TSC-40 scores) within studies similar to this one. RCI determines the participant's category of change post-intervention: recovered (i.e., met criteria for clinical change), improved (i.e., have statistically significant change but not large enough to be considered a full recovery), unchanged (i.e., no change over time), and deteriorated (i.e., significant worsening of symptoms over time).

The second hypothesis, that PE+ treatment will result in clinically significant reductions in negative psychotic symptoms (e.g., anhedonia); third hypothesis, that PE+ treatment will result in clinically significant reductions in the frequency and quantity of substance misuse; and fourth hypothesis, that global improvement in functioning from pre- to post-PE+ therapy will occur with gains maintained 2 months-post treatment, will also be addressed using the RCI.

The following table illustrates the scores necessary to obtain in order to be classified within the four RCI categories:

| | Adversity TSC-40 total score[1] | Psychotic sx: Positive PANSS[2**] | Psychotic sx: Negative PANSS[2] | Hopelessness BHS[4] | Avoidance BEAQ[5] | PCL-5 (8-item): Total score[6] |
|---|---|---|---|---|---|---|
| **Clinically significant change** | Post-treatment mean <18.25<br><br>Mean decreased from pre-treatment by at least 7.14 | Post-treatment mean < 8.57<br><br>Mean decreased from pre-treatment by at least 8.24 | Post-treatment mean < 9.72<br><br>Mean decreased from pre-treatment by at least 10.33 | Post-treatment mean < 4.41<br><br>Mean decreased from pre-treatment by at least 7.38 | Post-treatment mean < 49.83<br><br>Mean decreased from pre-treatment by at least 15.67 | Post-treatment score < 12.3<br><br>Score decreased from pre-treatment by at least 7.14 |
| **Improved** | Post-treatment mean > 18.25<br><br>Mean decreased from pre-treatment by at least 7.14 | Post-treatment mean > 8.57<br><br>Mean decreased from pre-treatment by at least 8.24 | Post-treatment mean > 9.72<br><br>Mean decreased from pre-treatment by at least 10.33 | Post-treatment mean > 4.41<br><br>Mean decreased from pre-treatment by at least 7.38 | Post-treatment mean > 49.83<br><br>Mean decreased from pre-treatment by at least 15.67 | Post-treatment score > 12.3<br><br>Score decreased from pre-treatment by at least 7.14 |
| **No change** | Mean decreased from pre-treatment by < 7.14 | Mean decreased from pre-treatment by < 8.24 | Mean decreased from pre-treatment by < 10.33 | Mean decreased from pre-treatment by < 7.38 | Mean decreased from pre-treatment by < 15.67 | Score decreased from pre-treatment by < 7.14 |
| **Deteriorated** | Mean increased from pre-treatment by at least 7.14 | Mean increased from pre-treatment by at least 8.24 | Mean increased from pre-treatment by at least 10.33 | Mean increased from pre-treatment by at least 7.38 | Mean increased from pre-treatment by at least 15.67 | Score increased from pre-treatment by at least 7.14 |

[1] – Mahato et al., 2017; 30 Indian people aged 18-45 with schizophrenia (clinical group) and 30 Indian people aged 18-45 with no psychiatric history (control group). All completed the TSC-40.

[2] – Baudin et al., 2016, 366 French people aged 15 to 84 with schizophrenia and schizoaffective disorder, 30% of whom have experienced childhood maltreatment and 27% of whom have a cannabis use disorder (clinical group); Frissen et al., 2018, 87 Dutch people aged 16-50 with no first-degree relatives with psychosis (control group). All completed the PANSS.

[3] – Hides et al., 2009; 102 Australian people with first episode psychosis (FEP) with a substance use disorder (clinical group) and 112 Australian people with FEP and no substance use disorder (control group). All participants aged 15-25. All completed the WHO ASSIST.

[4] – Goodby & MacLeod, 2016; 30 patients aged 19-35 with first-episode psychosis (clinical group) and 27 matched community participants aged 19-33 (control group). All completed the Beck Hopelessness Scale (BHS).

[5] – Gámez et al., 2014; 265 American outpatients aged 18-79 with various anxiety disorders and depression (clinical group) and 215 community members aged 24-67 (control group). All completed the BEAQ.

[6] – Pereira-Lima et al., (2019) as the clinical group (Brazilian psychiatric outpatients aged 18+) and scores from Geier and colleagues' (2020) PTSD negative group as the control group.

*Means are for each individual measure score; e.g., a mean of 8 on the PANSS is specific to that measure and carries different meaning on the ASSIST
** It is unlikely that participants will have such elevated positive symptoms/elevated positive symptom scores on the PANSS and be able to consent and participate in this study. However, it seems appropriate to use representative scores and form hypotheses in advance, as with any other symptom in this study. Therefore, little to no change, or a lack of clinically significant improvement, during this treatment may not be an indicator of a lack of effectiveness.

*Specific trauma symptom RCIs:*

| | TSC-40: Dissociation | TSC-40: Anxiety | TSC-40: Depression | TSC-40: Sexual abuse trauma index | TSC-40: Sleep disturbance | TSC-40: Sexual problems |
|---|---|---|---|---|---|---|
| **Clinically significant change** | Post-treatment mean < 3.71<br><br>Mean decreased from pre-treatment by at least 3.06 | Post-treatment mean < 3.12<br><br>Mean decreased from pre-treatment by at least 2.57 | Post-treatment mean < 2.02<br><br>Mean decreased from pre-treatment by at least 2.83 | Post-treatment mean < 2.81<br><br>Mean decreased from pre-treatment by at least 2.33 | Post-treatment mean < 1.66<br><br>Mean decreased from pre-treatment by at least 2.42 | Post-treatment mean < 0.51<br><br>Mean decreased from pre-treatment by at least 2 |
| **Improved** | Post-treatment mean > 3.71<br><br>Mean decreased from pre-treatment by at least 3.06 | Post-treatment mean > 3.12<br><br>Mean decreased from pre-treatment by at least 2.57 | Post-treatment mean > 2.02<br><br>Mean decreased from pre-treatment by at least 2.83 | Post-treatment mean > 2.81<br><br>Mean decreased from pre-treatment by at least 2.33 | Post-treatment mean > 1.66<br><br>Mean decreased from pre-treatment by at least 2.42 | Post-treatment mean > 0.51<br><br>Mean decreased from pre-treatment by at least 2 |
| **No change** | Mean decreased from pre-treatment by < 3.06 | Mean decreased from pre-treatment by < 2.57 | Mean decreased from pre-treatment by < 2.83 | Mean decreased from pre-treatment by < 2.33 | Mean decreased from pre-treatment by < 2.42 | Mean decreased from pre-treatment by < 2 |
| **Deteriorated** | Mean increased from pre-treatment by at least 3.06 | Mean increased from pre-treatment by at least 2.57 | Mean increased from pre-treatment by at least 2.83 | Mean increased from pre-treatment by at least 2.33 | Mean increased from pre-treatment by at least 2.42 | Mean increased from pre-treatment by at least 2 |

*All data in this table is based on Mahato et al., 2017. All participants are Indian adults aged 18-45. The clinical group participants (*N* = 30) were diagnosed with schizophrenia while the control group (*N* = 30) had no psychiatric history. All participants completed the TSC-40.

*Means are for each individual subscale score; e.g., a mean of 2 on the TSC-40 dissociation subscale is specific to that subscale and carries different meaning on the TSC-40 sleep disturbance or depression subscale.

*Functioning RCIs:*

| | Functioning: SOFAS[1] | Symptom improvement CGI-I[2] | Symptom severity CGI-S[3] |
|---|---|---|---|
| **Clinically significant change** | Post-treatment score > 73.31<br><br>Score increased from pre-treatment by at least 16.52 | Post-treatment score of 1 or 2 | Post-treatment score < 3.8<br><br>Score decreased from pre-treatment by at least 1.24 |
| **Improved** | Post-treatment score > 73.31<br><br>Score increased from pre-treatment by at least 16.52 | Post-treatment score of 3 | Post-treatment score > 3.8<br><br>Score decreased from pre-treatment by at least 1.24 |
| **No change** | Score decreased from pre-treatment by < 16.52 | Post-treatment score of 4 | Score decreased from pre-treatment by < 1.24 |
| **Deteriorated** | Score decreased from pre-treatment by at least 16.52 | Post-treatment score of 5,6, or 7 | Score increased from pre-treatment by at least 1.24 |

[1] – Thompson et al., 2012; 40 Australian people aged 15-25 years old with first-episode psychosis (clinical group) and 30 people aged 15-25 years old with no past or current psychiatric history (control group). All completed the SOFAS.
[2] – Given the structure of the CGI-I, improvement categories are already built into the instrument; therefore, we will use the pre-determined categories to establish significant change. Scoring is as follows: 0 (Not assessed), 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), and 7 (very much worse).
[3]– Segarra et al., 2012; 477 Spanish people aged 18-45 years with first-episode psychosis and a schizophrenia diagnosis (clinical group), and the same 477 people assessed 1 year into treatment (control group)

*Scores are for each individual measure score; e.g., a score of 6 on the SOFAS is specific to that measure and carries different scoring on the CGI-I or -S.

*ASSIST: Specific substance use RCIs:*

| | SU: Alcohol[1] | SU: Cannabis[2] | SU: Amphetamines[3] | SU: Hallucinogens[4] | SU: Opiates[5] | SU: Cocaine[a] | SU: Sedatives[a] |
|---|---|---|---|---|---|---|---|
| **Clinically significant change** | Post-treatment score < 4.76 | Post-treatment score < 4.63 | Post-treatment score < 2 | Post-treatment score < 0.22<br><br>Score decreased from pre- | Post-treatment score < 0.42 | Post-treatment score < 0.5 | Post-treatment score < 2.7 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Score decreased from pre-treatment by at least 6.05 | Score decreased from pre-treatment by at least 7.85 | Score decreased from pre-treatment by at least 7.33 | treatment by at least 0.87 | Score decreased from pre-treatment by at least 8.24 | Score decreased from pre-treatment by at least 7.02 | Score decreased from pre-treatment by at least 9.1 |
| **Improved** | Post-treatment score > 4.76<br><br>Score decreased from pre-treatment by at least 6.05 | Post-treatment score > 4.63<br><br>Score decreased from pre-treatment by at least 7.85 | Post-treatment score > 2<br><br>Score decreased from pre-treatment by at least 7.33 | Post-treatment score > 0.22<br><br>Score decreased from pre-treatment by at least 0.87 | Post-treatment score > 0.42<br><br>Score decreased from pre-treatment by at least 8.24 | Post-treatment score >0.5<br><br>Score decreased from pre-treatment by at least 7.02 | Post-treatment score >3<br><br>Score decreased from pre-treatment by at least 9.1 |
| **No change** | Score decreased from pre-treatment by < 6.05 | Score decreased from pre-treatment by < 7.85 | Score decreased from pre-treatment by < 7.33 | Score decreased from pre-treatment by < 0.87 | Score decreased from pre-treatment by < 8.24 | Score decreased from pre-treatment by < 7.02 | Score decreased from pre-treatment by < 9.1 |
| **Deteriorated** | Score increased from pre-treatment by at least 6.05 | Score increased from pre-treatment by at least 7.85 | Score increased from pre-treatment by at least 7.33 | Score increased from pre-treatment by at least 0.87 | Score increased from pre-treatment by at least 8.24 | Score increased from pre-treatment by at least 7.02 | Score increased from pre-treatment by at least 9.1 |

All data (except cocaine use data) is from Hides et al., 2009. All participants are Australian people aged 15-25; the clinical group for each substance below contains individuals with polysubstance use. All participants completed the WHO ASSIST and all substance use disorders were diagnosed using the SCID.

[1] – 45 people with an alcohol use disorder (clinical group) and 169 people without an alcohol use disorder (control group).
[2] – 80 people with a cannabis use disorder (clinical group) and 134 people without a cannabis use disorder (control group).
[3] – 27 people with a stimulant use disorder (clinical group) and 187 people without a stimulant use disorder (control group).
[4] – 16 people with a hallucinogen use disorder (clinical group) and 198 people without a hallucinogen use disorder (control group).
[5] – 8 people with an opiate use disorder (clinical group) and 206 people without an opiate use disorder (control group).

*Scores are for each individual subscale score, e.g., a score of 4 on the alcohol subscale of the ASSIST is specific to that subscale and carries different meaning on the cannabis or opiates subscale.

[a]Cocaine and sedative data are from Paruk, Jhazbhay, Singh, Sartorius, & Burns, 2018 (control group) and Carlyle, Constable, Walter, Wilson, Newland, & Hides, 2021 (clinical group).
*There is no calculation for 'other' substances given that this varies so widely as it is inclusive of many different substances

## Risks and Benefits

### Risks

There is a risk that participants will become distressed because the study involves asking participants to think about, discuss, and process difficult or upsetting events that have occurred in participants' lives. Previous research has suggested that asking patients about past adversity, although difficult, is often beneficial and ethical (Becker-Blease & Freyd, 2006); however, it is possible that participants' current psychotic symptoms, substance use, or adversity-related symptoms (e.g., anxiety, depression) may be worsened as a result of participation in this study. Previous research by van den Berg and colleagues (2016, 2018) suggest this risk of exacerbation is small, but present. Therefore, all participants will be informed of the risk of symptom worsening that may or may not be temporary. A safety measure will be put in place – if participants appear to significantly deteriorate in functioning or symptoms worsen significantly, their NSEPP clinician will be alerted to ensure they can monitor their patient and maintain the standard of care. Participants may also experience no change in their symptoms, which may be distressing and is a possible risk. All participants will be advised of this possibility and their explicit consent to speak with their clinician will be obtained prior to their participation in the study.

### Benefits

Participants may experience an improvement in their symptoms and/or functioning as a result of participating in this study; this benefit may be minor or significant. Participants may also indirectly benefit from participation by helping to optimize a trauma-focused treatment that people with EPP may benefit from in the future. Although there are risks involved in participating in this study, the benefits outweigh the risks in that the benefits are more likely to occur than the risks (van den Berg et al., 2015). In addition, participants may benefit from forming a therapeutic alliance with a therapist, which may increase the likelihood that participants will seek psychological support in the future if needed.

### Liability

Study materials will not suggest or indicate in any way that are attempting to limit liability to which we or the NSEPP would typically be subject.

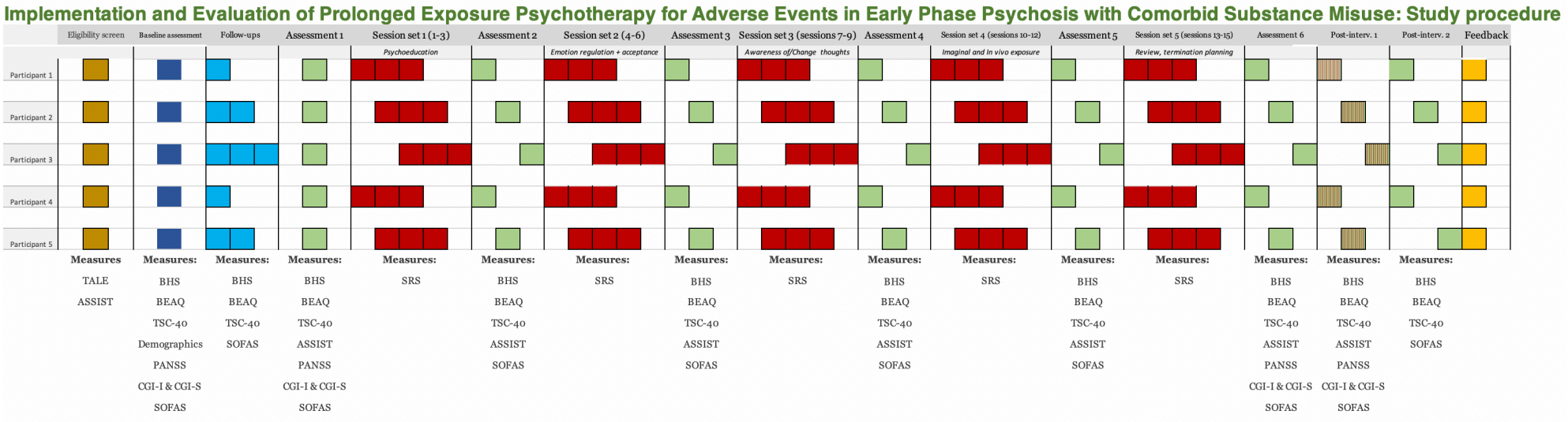


*Figure 1.* The study's multiple baseline design and procedures

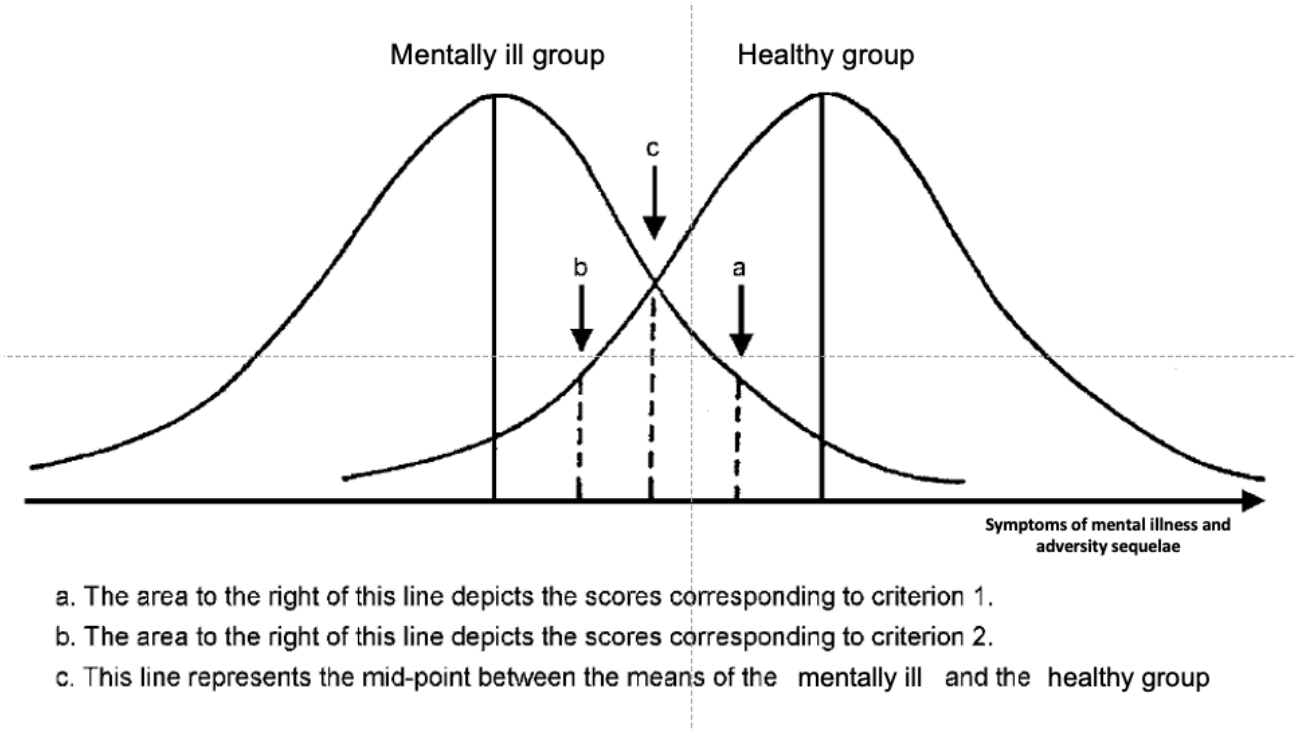


*Figure 2*. Reliable Change Index (RCI) change criterion

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