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# Assessment of patient life engagement in schizophrenia using items from the Positive and Negative Syndrome Scale

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ABSTRACT

*Background:* Improved patient life engagement is a meaningful treatment goal in schizophrenia that cannot be satisfactorily measured using existing tools. This research aimed to determine whether certain items from the Positive and Negative Syndrome Scale (PANSS) can assess patient life engagement in schizophrenia.
*Methods:* Three approaches were used to identify PANSS items that reflect patient life engagement: (1) a panel discussion with expert psychiatrists ($n = 4$); (2) interviews with patients with schizophrenia ($n = 20$); and (3) a principal component analysis to explore clustering of items ($n = 954$ from three randomized controlled trials). Internal consistency was assessed by Cronbach's alpha and item–total correlations. A minimal clinically important difference (MCID) was determined by anchor- and distribution-based methods.
*Results:* Expert psychiatrists identified 11 relevant items, and patients rated 13 items as "very relevant" to patient life engagement, most of which clustered in the principal component analysis. Considering all results, a composite set of 14 PANSS items that may be relevant to patient life engagement in schizophrenia was devised: P2, N1, N2, N3, N4, N5, N6, N7, G6, G7, G11, G13, G15, G16 (Cronbach's alpha, 0.84; item–total correlations, 0.35–0.56, indicating acceptable correlation with the underlying concept; exception: G6 [depression], 0.19). An MCID of 5 points (small/moderate improvement) or 10 points (large improvement) may be appropriate.
*Conclusions:* A subset of 14 PANSS items may be used to reflect patient life engagement in clinical practice/trials in schizophrenia, complementing the results of traditional psychiatric symptom scales with a patient-centered outcome that is relevant to real-world treatment goals.

## 1. Introduction

Patient 'life engagement' is a broad term that describes positive health aspects related to life fulfillment, well-being, and valued living across four domains: emotional (affect/mood), physical (energy), social (interest), and cognitive (alertness/thinking) (Bartrés-Faz et al., 2018; Weiss et al., 2021). Unlike physicians, who generally prioritize traditional treatment goals, patients with schizophrenia may value improved satisfaction and independence more than improvement of psychosis (Bridges et al., 2013). Thus, patient life engagement should be considered as a treatment goal in schizophrenia and monitored during treatment (Correll et al., 2022a,b).

Given the increasing importance placed on patient experience data (Weldring and Smith, 2013; Kieffer et al., 2020), patient life engagement would ideally be assessed using a patient-reported outcome measure. However, current patient-reported psychiatric rating scales do not

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satisfactorily capture patient life engagement (McIntyre et al., 2022), which is a barrier to using patient life engagement as a treatment goal. For example, the Engaged Living Scale and Life Engagement Test have not been validated in populations with psychiatric disorders, and largely overlook the physical and cognitive domains of patient life engagement (Scheier et al., 2006; Trompetter et al., 2013; McIntyre et al., 2022). A set of items from the Inventory of Depressive Symptomatology Self-Report (IDS-SR) was recently developed and validated to assess patient life engagement in major depressive disorder (Thase et al., 2023; Therrien et al., 2022). This 'IDS-$SR_{10}$ Life Engagement subscale' has been used as a co-primary outcome in an open-label, interventional study (Therrien et al., 2024), as well as in post hoc analyses of clinical trials (McIntyre et al., 2023). However, no such tool exists for use in schizophrenia.

The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) is considered the gold standard for assessing the efficacy of antipsychotic treatments in clinical trials in schizophrenia (Opler et al., 2017). The PANSS, a clinician-administered scale, comprises 30 items covering a broad range of symptoms that may overlap with aspects of patient life engagement (Kay et al., 1987; Weiss et al., 2021). The aim of this research was to determine whether certain items from the PANSS can be used to assess patient life engagement in schizophrenia.

## 2. Methods

Three approaches were used to identify items from the PANSS that reflect patient life engagement: (1) discussion with a panel of expert psychiatrists; (2) interviews with patients with schizophrenia; and (3) a principal component analysis (PCA). Upon selection of a set of items, psychometric analyses were performed to assess reliability, and a minimal clinically important difference (MCID) was determined.

### 2.1. Expert panel

In an informal panel discussion, four expert academic psychiatrists used a modified Delphi approach to select items from the PANSS that they considered suitable to capture patient well-being and engagement in all aspects of life, beyond the core symptoms of schizophrenia. Items were selected based on the psychiatrists' overall clinical impression, in consideration of the four-domain model of patient life engagement (Weiss et al., 2021).

### 2.2. Patient interview study

The aim of the patient interview study was to support the relevance and importance of the patient life engagement framework among individuals with schizophrenia, and to support the content validity of PANSS items to assess elements of this framework. Details of study design are provided in Appendix A. Briefly, 20 generally high-functioning outpatients aged ≥18 years with schizophrenia for ≥2 years were recruited in the US. Researchers at RTI Health Solutions conducted 60-minute phone/virtual interviews with individual participants using a semi-structured interview guide (provided in Appendix A). A "visual primer" tool (Fig. 1, developed from a prior patient interview study of patient life engagement in major depressive disorder (Therrien et al., 2022)) was used to assist participants' understanding of being engaged with life.

After general discussions on experiences with schizophrenia and life engagement, participants were shown a worksheet containing a list of the 30 PANSS items, with the following modifications: (1) the expert-identified patient-life-engagement items were presented first, to support the experts' selection (patients were pre-informed that these items were possibly relevant to patient life engagement) and to ensure that these items were covered as a priority within the allotted interview time; and (2) the PANSS is a clinician-administered scale that was not developed for patient use; consequently, the items and definitions were converted to patient-friendly, positively valenced terms (e.g., "conceptual disorganization" became "clear thinking and focus") to ease patient discussions (see Table A.1 in Appendix A). The patient-friendly terms were developed by two experienced psychologists at RTI Health Solutions, each with clinical and diagnostic experience in schizophrenia. Participants were asked to rate the 30 PANSS items according to their relevance to patient life engagement using a 3-point scale: 0 (not at all relevant), 1 (somewhat relevant), and 2 (very relevant), and to justify their ratings. These data were analyzed using descriptive statistics. After completing the rating exercise, participants were asked if anything was missing from the 30 PANSS items that they believed to be relevant to patient life engagement.

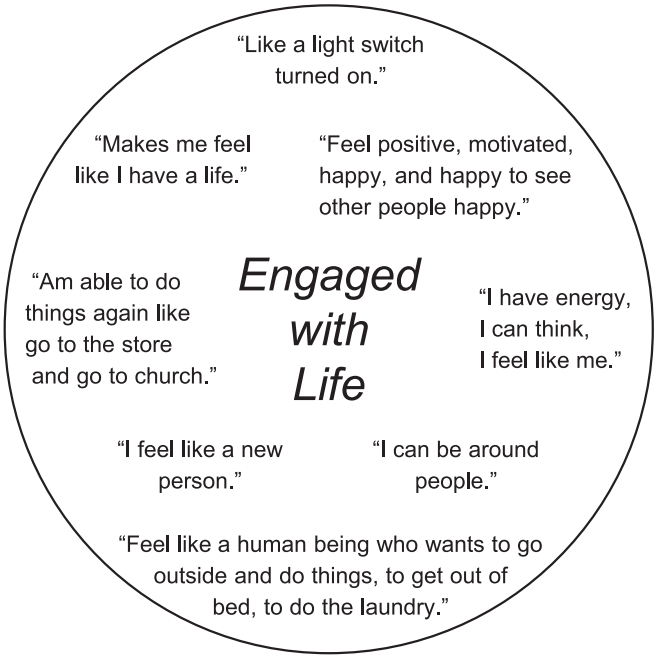


**Fig. 1.** "Engaged with life" visual primer.

### 2.3. Data source for PCA, psychometric, and MCID analyses

The PCA, psychometric, and MCID analyses used data from the Phase 3 clinical program of brexpiprazole, an atypical antipsychotic, for the treatment of schizophrenia. Data were included from three similarly designed, 6-week, randomized, double-blind, placebo-controlled trials of brexpiprazole in patients with acute schizophrenia conducted from July 2011 to December 2014 in Asia, Europe, North America, and South America (ClinicalTrials.gov identifiers: NCT01396421 (Correll et al., 2015), NCT01393613 (Kane et al., 2015), and NCT01810380 (Marder et al., 2017; Marder et al., 2020)). The trials were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice Guideline, and local regulatory requirements. The trial protocols were approved by relevant institutional review boards and independent ethics committees. All patients provided written informed consent after the nature of the procedures had been fully explained.

Detailed trial designs and results have been published (Correll et al., 2015; Kane et al., 2015; Marder et al., 2017). Briefly, patients aged 18–65 years experiencing an acute exacerbation of schizophrenia (American Psychiatric Association, 2000) were randomized to 6 weeks of double-blind treatment with placebo, brexpiprazole (fixed-dose 0.25, 1, 2, or 4 mg/day or flexible-dose 2–4 mg/day, depending on the trial), or active reference (quetiapine extended-release, one trial only). Patients remained in hospital for the duration of double-blind treatment. The primary endpoint in each trial was change from baseline to Week 6

in PANSS total score, which ranges from 30 (best) to 210 (worst), where each item is scored from 1 (absent) to 7 (extreme) (Kay et al., 1987).

The present analyses were not treatment specific: data for brexpiprazole and placebo were pooled together. However, data for low doses of brexpiprazole (0.25 and 1 mg/day) and for quetiapine were excluded since these arms were small and each was in one trial only (Correll et al., 2015; Kane et al., 2015; Marder et al., 2017).

### 2.4. PCA and clustering

PCAs are used to reduce a data set with many variables to a data set with a smaller number of independent (i.e., uncorrelated) variables (Jolliffe, 2002). This simplification allows patterns in the data to be identified more easily. In the present research, a PCA was performed to determine which PANSS items cluster together, to help identify groups of related items, and thereby to corroborate the expert- and patient-identified sets of life engagement items. The inputted variables were changes in PANSS item scores from baseline to trial endpoint. The resulting PCA plot was visually inspected to determine if the items selected by patients and clinicians clustered together.

### 2.5. Composite set of PANSS items

A composite set of items derived from the PANSS that may be relevant to patient life engagement in schizophrenia was formed based on items that were considered relevant by at least two of the following three methods (post hoc criteria): (1) selected by the expert panel; (2) rated as 2 (very relevant) by >50 % of patients in interviews (i.e., a median relevance of 2); (3) clustered by visual inspection in the PCA.

### 2.6. Psychometric analyses

Psychometric analyses were conducted to assess the reliability of the expert-identified, patient-identified, and composite sets of items, and the full 30-item PANSS. Specifically, Cronbach's alpha and item–total correlations were calculated to estimate the internal consistency of each set of items. Cronbach's alpha describes the extent to which all the items in a test measure the same concept, expressed as a number between 0 and 1, where 0.70–0.90 is generally acceptable (Tavakol and Dennick, 2011). Item–total correlations are the correlation of a particular item with a scale composed of all other items, where >0.3 is widely regarded as an acceptable correlation with the underlying concept. Analyses were performed using data for change from baseline to Week 6 (to align with the PCA), and separately using baseline data as a sensitivity analysis.

A confirmatory factor analysis was performed to compare two-factor (patient-life-engagement items versus all other items) and one-factor (all items) models, where a smaller Bayesian information criterion (BIC) indicates a better fitting model (Adachi, 2016).

Convergent validity of the PANSS patient-life-engagement items with the PANSS Prosocial subscale, which may measure social aspects of patient life engagement (Purnine et al., 2000; Baran and Docherty, 2008; Docherty et al., 2010), was assessed using Spearman correlations between score changes from baseline to Week 6. The original 6-item (G16, N2, N4, N7, P3, P6) and modified 4-item (G16, N2, N4, N5) Prosocial subscales were considered.

### 2.7. Minimal clinically important difference

The MCID of the composite set of 14 PANSS items that may be relevant to patient life engagement was estimated using two anchor-based approaches (a linear regression model and receiver operating characteristic curves) and a distribution-based approach. Full MCID methods are provided in Appendix B.

The Clinical Global Impressions – Severity of illness (CGI-S) scale, a secondary efficacy measure in the brexpiprazole Phase 3 trials, was used as the anchor. The CGI-S comprises a single item rated from 1 (normal, not at all ill) to 7 (among the most extremely ill patients) (Guy, 1976). To confirm the relevance of the CGI-S as an anchor, (1) the Spearman correlation was calculated between change from baseline to Week 6 in CGI-S score and score on the composite set of PANSS items; and (2) mean change from baseline to trial endpoint in score on the composite set of PANSS items was investigated by CGI-S score change category over the same period (improved by ≥3 points, improved by 2 points, improved by 1 point, no change, and worsened by ≥1 point).

Results from anchor- and distribution-based methods were triangulated to determine an MCID.

### 2.8. Software

All analyses were performed using R-4.2.2 (R Core Team, 2022), with the packages *psych*, *emmeans* and *cutpointr*.

## 3. Results

### 3.1. Expert psychiatrist selection of patient-life-engagement items

The expert psychiatrists identified the following 11 items from the PANSS that they considered suitable to capture patient life engagement in schizophrenia: blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4), difficulty in abstract thinking (N5), lack of spontaneity and flow of conversation (N6), depression (G6), motor retardation (G7), disturbance of volition (G13), preoccupation (G15), and active social avoidance (G16), where codes in parentheses indicate item numbers on the PANSS Negative (N) and General psychopathology (G) subscales.

### 3.2. Patient selection of patient-life-engagement items

Twenty patients were interviewed from March 13 to 30, 2023. The sample had a mean (standard deviation [SD]) age of 44.3 (10.7) years, was 65 % female, 45 % African American or Black, and 35 % White, and had a mean (SD) time since diagnosis of 14.7 (9.8) years (Table A.2 in Appendix A). Antipsychotics with reported current use by ≥25 % of patients were risperidone (30 %) and aripiprazole (25 %); four patients (20 %) reported current use of more than one antipsychotic medication (Table A.2 in Appendix A).

Almost all patients ($n = 19$) said that the "engaged with life" term resonated with them; specifically, that they could identify times in their lives when they felt engaged with life. The one other patient required additional discussion and prompting to elaborate on their understanding and experience with feeling engaged with life. In describing their experiences with feeling engaged with life, all patients covered all four domains of patient life engagement (following targeted questioning, if not spontaneously reported).

Patient relevance ratings for all items of the PANSS are shown in Table 1. Thirteen items were rated 2 ("very relevant" to patient life engagement) by >50 % of patients, and thus also had a median score of 2. These 13 patient-selected items included 10 of the 11 expert-identified items; the exception was difficulty in abstract thinking (N5), rated 2 by 35 % of patients. The three items identified by patients but not psychiatrists were: (1) poor attention (G11) – the most relevant item for patients, rated 2 by 85 %; (2) conceptual disorganization (P2) – the only item selected from the Positive (P) subscale of the PANSS; and (3) stereotyped thinking (N7).

When asked if any important aspects of patient life engagement were missing from the PANSS, patients suggested the following aspects: motivation, productivity, and proactivity ($n = 5$); having focus ($n = 1$); treating others like you want to be treated ($n = 1$); increased confidence ($n = 1$); distinguishing reality versus nonreality ($n = 1$); and how you feel about taking medication ($n = 1$). The authors believe that most of these aspects are covered by existing PANSS items – see '4. Discussion' for details.

**Table 1**
Patient ratings of the relevance of PANSS items to patient life engagement.

| PANSS item[a] | Positively valenced interview concept | Median relevance rating | Patient rating, n (%) | | |
|---|---|---|---|---|---|
| | | | 0: Not at all relevant | 1: Somewhat relevant | 2: Very relevant |
| Delusions (P1) | Reasonable beliefs (no delusions) | 1.5 | 8 (40) | 2 (10) | 10 (50) |
| Conceptual disorganization (P2) | Clear thinking and focus | 2 | 1 (5) | 5 (25) | 14 (70) |
| Hallucinatory behavior (P3) | No hallucinations | 1 | 9 (45) | 6 (30) | 5 (25) |
| Excitement (P4) | Appropriate physical and emotional reactions | 1 | 1 (5) | 10 (50) | 9 (45) |
| Grandiosity (P5) | Appropriate sense of self | 0 | 14 (70) | 1 (5) | 5 (25) |
| Suspiciousness/persecution (P6) | Trust | 1 | 9 (45) | 9 (45) | 2 (10) |
| Hostility (P7) | Calm | 1 | 9 (45) | 4 (20) | 7 (35) |
| **Blunted affect (N1)** | **Emotional responsiveness** | **2** | **0 (0)** | **6 (30)** | **14 (70)** |
| **Emotional withdrawal (N2)** | **Emotional involvement** | **2** | **0 (0)** | **5 (25)** | **15 (75)** |
| **Poor rapport (N3)** | **Rapport with others** | **2** | **1 (5)** | **8 (40)** | **11 (55)** |
| **Passive/apathetic social withdrawal (N4)** | **Social interest** | **2** | **1 (5)** | **7 (35)** | **12 (60)** |
| **Difficulty in abstract thinking (N5)** | **Abstract thinking** | **1** | **3 (15)** | **10 (50)** | **7 (35)** |
| **Lack of spontaneity and flow of conversation (N6)** | **Spontaneity and flow of conversation** | **2** | **2 (10)** | **6 (30)** | **12 (60)** |
| Stereotyped thinking (N7) | Flexible thinking | 2 | 1 (5) | 6 (30) | 13 (65) |
| Somatic concern (G1) | Realistic bodily concerns | 0 | 14 (70) | 2 (10) | 4 (20) |
| Anxiety (G2) | Mental peace | 1 | 5 (25) | 6 (30) | 9 (45) |
| Guilt feelings (G3) | No self-blame | 1 | 9 (45) | 5 (25) | 6 (30) |
| Tension (G4) | Bodily peace | 1 | 2 (10) | 9 (45) | 9 (45) |
| Mannerisms and posturing (G5) | Natural body movements | 0.5 | 10 (50) | 5 (25) | 5 (25) |
| **Depression (G6)** | **Feeling content** | **2** | **1 (5)** | **6 (30)** | **13 (65)** |
| **Motor retardation (G7)** | **Appropriate motor activity** | **2** | **4 (20)** | **5 (25)** | **11 (55)** |
| Uncooperativeness (G8) | Easy-going | 1 | 8 (40) | 4 (20) | 8 (40) |
| Unusual thought content (G9) | Usual thought content | 1 | 7 (35) | 6 (30) | 7 (35) |
| Disorientation (G10) | Oriented | 0 | 12 (60) | 2 (10) | 6 (30) |
| Poor attention (G11) | Attention | 2 | 0 (0) | 3 (15) | 17 (85) |
| Lack of judgment and insight (G12) | Insight | 0 | 11 (55) | 1 (5) | 8 (40) |
| **Disturbance of volition (G13)** | **Control** | **2** | **3 (15)** | **4 (20)** | **13 (65)** |
| Poor impulse control (G14) | Impulse control | 1 | 4 (20) | 8 (40) | 8 (40) |
| **Preoccupation (G15)** | **External focus** | **2** | **4 (20)** | **4 (20)** | **12 (60)** |
| **Active social avoidance (G16)** | **Social approach** | **2** | **3 (15)** | **6 (30)** | **11 (55)** |

PANSS: Positive and Negative Syndrome Scale.
[a] Items in bold represent those selected by the expert panel as relevant to patient life engagement.

### 3.3. Patient data for the PCA, psychometric, and MCID analyses

The PCA, psychometric, and MCID analyses included pretreatment (baseline) data for 1385 patients, and on-treatment (change from baseline to trial endpoint) data for 954 patients. The sample of 954 patients had a mean (SD) age of 40.0 (10.7) years, was 39.0 % female, and 68.4 % White (Table A.3 in Appendix A). On average, patients were markedly ill at baseline, with a mean (SD) CGI-S score of 4.9 (0.6) and a mean (SD) PANSS total score of 95.9 (12.3).

### 3.4. PCA and clustering

One clear axis (PC1) emerged in the PCA with an eigenvalue of 8.01, which explained 26.7 % of the total variance. The next highest eigenvalue (for PC2) was 2.32, which cumulatively explained 34.4 % of the total variance. Overall, six axes had eigenvalues >1, cumulatively explaining 51.3 % of the total variance.

PCA data were plotted using the first two eigenvectors (Fig. 2). Visual assessment of clustering showed that all of the expert- and patient-identified items clustered together, except for depression (G6) and motor retardation (G7).

### 3.5. Composite set of PANSS items

Fourteen PANSS items were identified as relevant to patient life engagement in at least two of the three methods used (expert panel, patient interviews, and PCA), and were therefore selected as the composite set of PANSS items that may be relevant to patient life engagement in schizophrenia (Table 2).

### 3.6. Psychometric analyses

Based on the pooled clinical trial data, Cronbach's alpha using change from baseline data was 0.80 for the 11 expert-identified items, 0.83 for the 13 patient-identified items, 0.84 for the composite set of 14 PANSS items that may be relevant to patient life engagement, and 0.90 for the full 30-item PANSS.

Item–total correlations calculated using change from baseline data were >0.3 for 13 of the 14 PANSS items in the composite set (Table 3), indicating acceptable correlation with the underlying concept. The highest correlations in the composite set were for passive/apathetic social withdrawal (N4) (0.56), emotional withdrawal (N2) (0.55), and preoccupation (G15) (0.53). Depression (G6) was not considered a good fit, with a correlation of 0.19 with the composite set of items.

Using baseline data (sensitivity analysis), Cronbach's alpha was 0.75 for the 11 expert-identified items, 0.79 for the 13 patient-identified items, 0.79 for the composite set of items, and 0.78 for the full 30-item PANSS. Item–total correlations calculated using baseline data were >0.3 for 12 of the 14 items in the composite set; the exceptions were depression (G6) (−0.05) and active social avoidance (G16) (0.23) (data not shown).

In the confirmatory factor analysis, the two-factor model had a smaller BIC (80,683.25) than the one-factor model (81,090.14; difference, 406.89), indicating that the model with the proposed patient-life-engagement items had a better fit.

Strong correlations were observed between change from baseline to Week 6 in scores on the composite set of PANSS patient-life-engagement items and the PANSS Prosocial subscale (Spearman's $\rho = 0.81$ for original and modified versions).

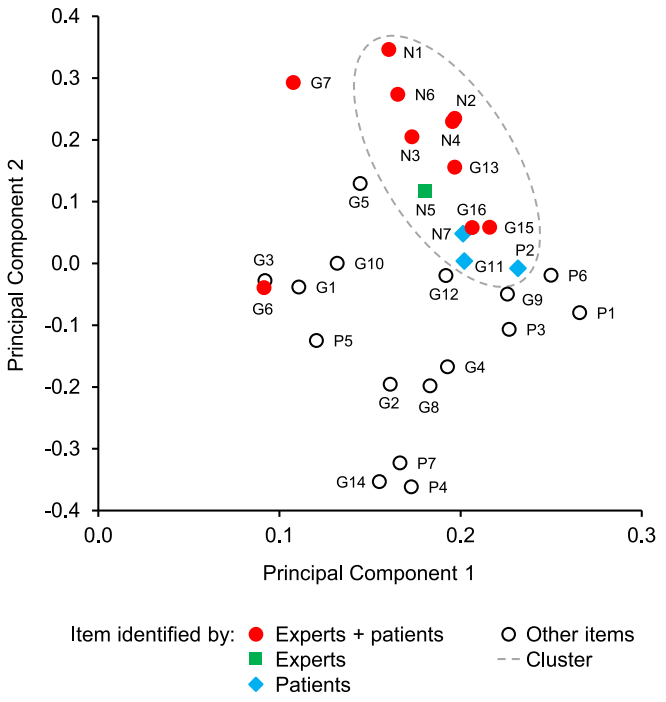


**Fig. 2.** Principal component analysis of PANSS items, utilizing data for change from baseline to trial endpoint ($n$ = 954 patients from three randomized controlled trials of brexpiprazole in patients with schizophrenia who had a measurement at baseline and Week 6 for each PANSS item). Labels correspond to PANSS item codes. Solid data points represent items considered related to patient life engagement by the expert panel and/or patient interviews. The dashed oval indicates items that visually cluster together. PANSS: Positive and Negative Syndrome Scale.

### 3.7. Minimal clinically important difference

Change from baseline to Week 6 in score on the composite set of 14 PANSS items that may be relevant to patient life engagement showed good correlation with change in CGI-S score (Spearman's ρ = 0.67), justifying the use of the CGI-S as an anchor. Furthermore, improvement in the composite set of 14 PANSS items increased with CGI-S score change category (Fig. 3), with mean (SD) improvements of −19.2 (8.7) among patients who improved by ≥3 points on the CGI-S, −12.3 (6.7) among patients who improved by 2 points, −7.8 (5.4) among patients who improved by 1 point, −1.7 (4.8) among patients with no change in CGI-S score, and +7.6 (9.1) among patients who worsened on the CGI-S.

In the anchor-based linear model, MCID estimates using a more conservative assumption (i.e., a 2-point improvement in CGI-S score versus no change) corresponded to a change of −10.5 points in the composite set of 14 PANSS items. Using less conservative assumptions (i.e., a 1-point improvement in CGI-S score), MCID estimates ranged from −4.4 to −6.1 points. In the anchor-based receiver operating characteristic model, the optimal cut-off for a 2-point improvement in CGI-S score versus no change was −5.5 points. In the distribution-based approach, the standard error of measurement for the composite set of 14 PANSS items at baseline was 2.9; a more conservative threshold of 1.96 standard errors of measurement (Rai et al., 2015) suggested an MCID of 5.7. Full MCID results are provided in Appendix B.

## 4. Discussion

In this analysis, a panel of expert psychiatrists, a patient interview study and a PCA generally aligned in the identification of items from the PANSS (a clinician-administered scale) that may be relevant to assessing patient life engagement in people with schizophrenia. However, some discrepancies between approaches were identified and addressed, as follows. First, experts and the PCA (but not patients) identified difficulty in abstract thinking (N5) as part of the item set. Patients may have excluded this item because they believe it is possible to be engaged with life regardless of abstract thinking skills. Alternatively, patients may have excluded abstract thinking due to anosognosia (i.e., being unable or refusing to recognize that they have impaired abstract thinking). Second, patients and the PCA (but not experts) included three additional items from the cognitive domain of patient life engagement: conceptual disorganization (P2), stereotyped thinking (N7), and poor attention (G11). The authors agree that these items are relevant and should be included among the life engagement items. Third, experts and patients (but not the PCA) identified depression (G6) and motor retardation (G7) as relevant to patient life engagement. Item–total correlations supported the inclusion of motor retardation but found that depression was not a good fit with the other patient-life-engagement items. This result highlights that patient life engagement is a different concept to depression; that, while strongly linked, patient life engagement and depression are neither synonymous nor interchangeable terms (Thase et al., 2023). However, the importance of incorporating the patient voice into the development of clinical trial outcomes is widely recognized (European Medicines Agency, 2020; Hunter et al., 2015; Kieffer et al., 2020; Weldring and Smith, 2013); as such, the decision was made to retain depression – which was also selected by experts – among the life engagement items.

Considering all approaches, a composite set of 14 PANSS items that may be relevant to patient life engagement in schizophrenia was identified (Table 2). Psychometric analyses using change from baseline data supported the reliability of the composite set of items, except for

**Table 2**
The composite set of 14 PANSS items that may be relevant to patient life engagement in schizophrenia.

| PANSS item | Domain of patient life engagement | Expert-identified | Patient-rated[a] | PCA cluster | Number of methods selected by |
|---|---|---|---|---|---|
| Conceptual disorganization (P2) | Cognitive | – | ✓ | ✓ | 2 |
| Blunted affect (N1) | Emotional | ✓ | ✓ | ✓ | 3 |
| Emotional withdrawal (N2) | Emotional | ✓ | ✓ | ✓ | 3 |
| Poor rapport (N3) | Social | ✓ | ✓ | ✓ | 3 |
| Passive/apathetic social withdrawal (N4) | Social | ✓ | ✓ | ✓ | 3 |
| Difficulty in abstract thinking (N5) | Cognitive | ✓ | – | ✓ | 2 |
| Lack of spontaneity and flow of conversation (N6) | Social | ✓ | ✓ | ✓ | 3 |
| Stereotyped thinking (N7) | Cognitive | – | ✓ | ✓ | 2 |
| Depression (G6) | Emotional | ✓ | ✓ | – | 2 |
| Motor retardation (G7) | Physical | ✓ | ✓ | – | 2 |
| Poor attention (G11) | Cognitive | – | ✓ | ✓ | 2 |
| Disturbance of volition (G13) | Physical | ✓ | ✓ | ✓ | 3 |
| Preoccupation (G15) | Cognitive | ✓ | ✓ | ✓ | 3 |
| Active social avoidance (G16) | Social | ✓ | ✓ | ✓ | 3 |

PANSS: Positive and Negative Syndrome Scale; PCA: principal component analysis.
[a] Rated 2 (very relevant) by >50 % of patients.

**Table 3**
Item–total correlations for the expert-identified, patient-identified, and composite sets of PANSS items that may be relevant to patient life engagement, and the full 30-item PANSS, utilizing data for change from baseline to trial endpoint (n = 954).

| PANSS item | Expert-identified | Patient-rated[a] | 14-item composite set | All 30 items |
|---|---|---|---|---|
| Delusions (P1) | | | | 0.71 |
| Conceptual disorganization (P2) | | 0.49 | 0.51 | 0.60 |
| Hallucinatory behavior (P3) | | | | 0.58 |
| Excitement (P4) | | | | 0.45 |
| Grandiosity (P5) | | | | 0.30 |
| Suspiciousness/ persecution (P6) | | | | 0.65 |
| Hostility (P7) | | | | 0.44 |
| Blunted affect (N1) | 0.53 | 0.50 | 0.51 | 0.39 |
| Emotional withdrawal (N2) | 0.56 | 0.56 | 0.55 | 0.50 |
| Poor rapport (N3) | 0.47 | 0.48 | 0.49 | 0.43 |
| Passive/apathetic social withdrawal (N4) | 0.57 | 0.56 | 0.56 | 0.49 |
| Difficulty in abstract thinking (N5) | 0.41 | | 0.46 | 0.45 |
| Lack of spontaneity and flow of conversation (N6) | 0.50 | 0.51 | 0.51 | 0.40 |
| Stereotyped thinking (N7) | | 0.48 | 0.49 | 0.51 |
| Somatic concern (G1) | | | | 0.28 |
| Anxiety (G2) | | | | 0.42 |
| Guilt feelings (G3) | | | | 0.24 |
| Tension (G4) | | | | 0.51 |
| Mannerisms and posturing (G5) | | | | 0.36 |
| Depression (G6) | 0.20 | 0.20 | 0.19 | 0.24 |
| Motor retardation (G7) | 0.37 | 0.36 | 0.35 | 0.26 |
| Uncooperativeness (G8) | | | | 0.47 |
| Unusual thought content (G9) | | | | 0.58 |
| Disorientation (G10) | | | | 0.33 |
| Poor attention (G11) | | 0.48 | 0.49 | 0.51 |
| Lack of judgment and insight (G12) | | | | 0.48 |
| Disturbance of volition (G13) | 0.48 | 0.51 | 0.52 | 0.49 |
| Poor impulse control (G14) | | | | 0.40 |
| Preoccupation (G15) | 0.48 | 0.52 | 0.53 | 0.56 |
| Active social avoidance (G16) | 0.49 | 0.50 | 0.50 | 0.52 |

PANSS: Positive and Negative Syndrome Scale.
[a] Rated 2 (very relevant) by >50 % of patients.

depression (G6), as discussed above. Confirmatory factor analysis also supported the item selection. The composite set of items correlated strongly with the PANSS Prosocial subscale, as would be expected given that 4/6 items (original version) and 4/4 items (modified version) in the Prosocial subscale overlapped with the 14 patient-life-engagement items. Prior to the development of the composite set, the 11 expert-identified PANSS items were shown to correlate to varying degrees with schizophrenia severity, depression severity, functioning, cognition, and social ability in a study of 361 people with schizophrenia living in the community (Vita et al., 2023). In the context of the four-domain model of patient life engagement (Weiss et al., 2021), the composite set of items encompasses the emotional, physical, social, and cognitive domains.

Patients identified six additional aspects of patient life engagement that they thought were missing from the PANSS. In the opinion of the authors, four of these aspects (each mentioned by 1 patient) are covered by existing PANSS items (all in the composite set of 14 patient-life-engagement items, except where specified): 'having focus' is covered by conceptual disorganization (P2) and poor attention (G11); 'treating others like you want to be treated' is covered by poor rapport (N3); 'increased confidence' is covered by depression (G6); and

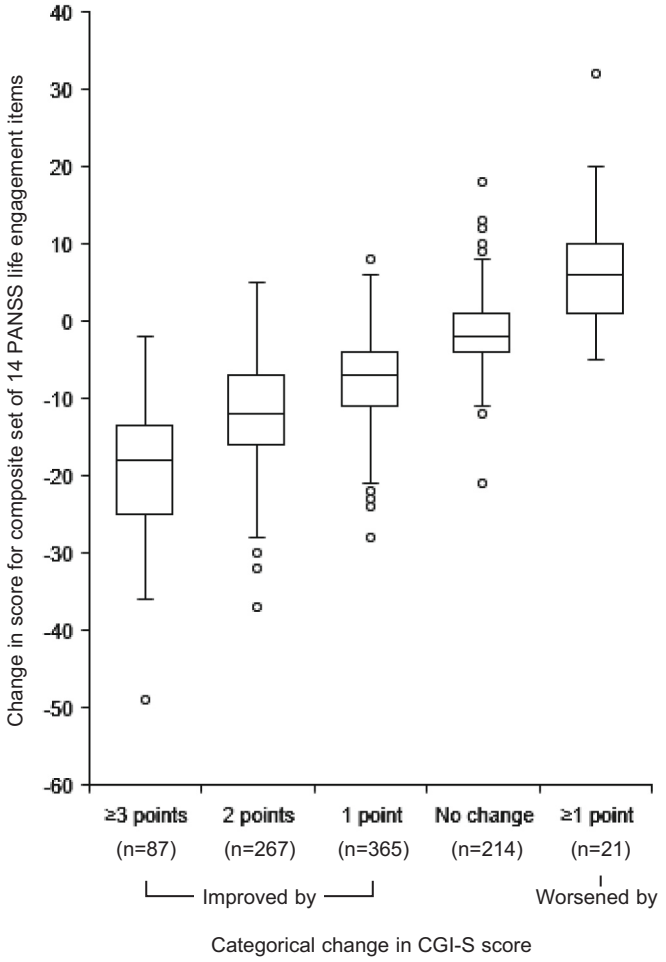


**Fig. 3.** Change from baseline to trial endpoint in the composite set of 14 PANSS items that may be relevant to patient life engagement, by CGI-S anchor category. CGI-S: Clinical Global Impressions – Severity of illness; PANSS: Positive and Negative Syndrome Scale.

'distinguishing reality versus nonreality' is covered by various items on the Positive subscale (outside of the composite set). A fifth aspect, 'motivation, productivity, and proactivity', is not specifically covered, but is reflected in various PANSS patient-life-engagement items including emotional withdrawal (N2) and disturbance of volition (G13). The sixth aspect, 'how you feel about taking medication' (mentioned by 1 patient), is not covered by existing items.

Due to the high value placed on life engagement by patients with schizophrenia, the composite set of 14 PANSS items may be useful in clinical practice to monitor patients' progress and assess treatment benefits that reflect the functional outcomes of life fulfillment, well-being, and participation in valued and meaningful activities (Bartrés-Faz et al., 2018; Weiss et al., 2021). The patient-life-engagement items may also be informative in clinical trials in schizophrenia to supplement measures of psychotic symptoms, and thereby to help identify treatments for schizophrenia that are particularly valued by patients. To assist in the interpretation of the clinical relevance of score changes, triangulation of results from anchor- and distribution-based methods suggested an MCID of 5 points (representing a small/moderate improvement) or 10 points (representing a large improvement) for the composite set of 14 PANSS items.

Strengths of this research are the incorporation of the patient voice to supplement expert- and data-driven approaches. Limitations include using the PANSS as a starting point, which was not developed to measure patient life engagement, and which is clinician-reported rather than

patient-reported. The expert panel comprised four participants, all North American physicians. Regarding the patient interview study, all patients were in the US and were generally high functioning (limiting generalizability to a broader patient population), there was possible bias towards higher ratings for the 11 expert-selected items because patients were pre-informed of their relevance, and patients considered positively valenced patient-friendly terms (to increase the accessibility of the scale) rather than actual PANSS terminology. Regarding the use of data from clinical trials, eligibility criteria and other restrictions limit generalizability, and there is a need to consider patient life engagement from different socioeconomic and cultural backgrounds, and at different stages of schizophrenia (of note, the clinical trial data were from hospitalized patients, whereas the patient interview data were from non-hospitalized patients).

Future research should involve development (with patient involvement) of a patient-reported instrument to measure the four-domain framework of patient life engagement, which could be validated against the presently identified set of PANSS items.

## 5. Conclusions

This analysis has shown the potential of a subset of 14 PANSS items to reflect patient life engagement in schizophrenia. Content validity of the items was determined by expert discussion and patient interviews. A data-driven PCA generally supported the item selection, and psychometric analyses demonstrated high internal consistency for all items except depression. The selected items may be used in clinical practice and trials to complement the results of traditional psychiatric symptom scales with a patient-centered outcome that is relevant to real-world treatment goals.

## CRediT authorship contribution statement

**Zahinoor Ismail:** Writing – review & editing, Methodology, Conceptualization. **Stine R. Meehan:** Writing – review & editing, Visualization, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Anja Farovik:** Writing – review & editing, Visualization, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Maia Miguelez:** Writing – review & editing, Visualization, Supervision, Methodology, Investigation, Conceptualization. **Shivani Kapadia:** Writing – review & editing, Supervision, Methodology. **Stephane Alexandre Regnier:** Writing – review & editing, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Zhen Zhang:** Writing – review & editing, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **T. Michelle Brown:** Writing – review & editing, Resources, Methodology, Investigation, Formal analysis. **Mirline Milien:** Writing – review & editing, Resources, Methodology, Investigation, Formal analysis. **Roger S. McIntyre:** Writing – review & editing, Methodology, Conceptualization.

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## Declaration of competing interest

Zahinoor Ismail has received grant support from CIHR, NIH, Brain Canada, and Weston Foundation, and has served as a consultant for Eisai, Eli Lilly, Lundbeck, Novo Nordisk, Otsuka and Roche. Zahinoor Ismail is also supported by the UK National Institute for Health and Care Research Exeter Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Stine R. Meehan, Anja Farovik, and Stephane Alexandre Regnier are full-time employees of H. Lundbeck A/S.

Maia Miguelez was a full-time employee of Otsuka Pharmaceutical Development & Commercialization Inc. at the time of this work.

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## Appendix A and Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2024.10.008.

## Data availability

To submit inquiries related to Otsuka clinical research, or to request access to individual participant data (IPD) associated with any Otsuka clinical trial, please visit https://clinical-trials.otsuka.com/. For all approved IPD access requests, Otsuka will share anonymized IPD on a remotely accessible data sharing platform.

## References

Adachi, K., 2016. Confirmatory factor analysis. In: Matrix-Based Introduction to Multivariate Data Analysis. Springer, Singapore, pp. 145–160.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. American Psychiatric Association, Washington, DC.

Baran, X.Y., Docherty, J.P., 2008. The "A" effect of aripiprazole. Presented at the American Psychiatric Association meeting. Washington, DC, May 3–8 2008. Downloaded from. https://www.psychiatry.org/getattachment/7edfa602-d33c-4f33-8e75-828b43af1e40/am_newresearch_2008.pdf. (Accessed 3 July 2024).

Bartrés-Faz, D., Cattaneo, G., Solana, J., Tormos, J.M., Pascual-Leone, A., 2018. Meaning in life: resilience beyond reserve. Alzheimers Res. Ther. 10, 47. https://doi.org/10.1186/s13195-018-0381-z.

Bridges, J.F.P., Slawik, L., Schmeding, A., Reimer, J., Naber, D., Kuhnigk, O., 2013. A test of concordance between patient and psychiatrist valuations of multiple treatment goals for schizophrenia. Health Expect. 16, 164–176. https://doi.org/10.1111/j.1369-7625.2011.00704.x.

Correll, C.U., Skuban, A., Ouyang, J., Hobart, M., Pfister, S., McQuade, R.D., Nyilas, M., Carson, W.H., Sanchez, R., Eriksson, H., 2015. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled trial. Am. J. Psychiatry 172, 870–880. https://doi.org/10.1176/appi.ajp.2015.14101275.

Correll, C.U., Ismail, Z., McIntyre, R.S., Rafeyan, R., Thase, M.E., 2022a. Patient functioning and life engagement: unmet needs in major depressive disorder and schizophrenia. J. Clin. Psychiatry 83, LU21112AH1. https://doi.org/10.4088/jcp.Lu21112ah1.

Correll, C.U., Ismail, Z., McIntyre, R.S., Rafeyan, R., Thase, M.E., 2022b. Patient functioning, life engagement, and treatment goals in schizophrenia. J. Clin. Psychiatry 83, LU21112AH2. https://doi.org/10.4088/jcp.Lu21112ah2.

Docherty, J.P., Baker, R.A., Eudicone, J., Mathew, S., Marcus, R.N., McQuade, R.D., Mankoski, R., 2010. Effect of aripiprazole versus haloperidol on PANSS Prosocial items in early-episode patients with schizophrenia. Schizophr. Res. 120, 199–203. https://doi.org/10.1016/j.schres.2010.03.040.

European Medicines Agency, 2020. ICH Reflection Paper on Proposed ICH Guideline Work to Advance Patient Focused Drug Development. European Medicines Agency, Amsterdam, The Netherlands. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-reflection-paper-proposed-ich-guideline-work-advance-patient-focused-drug-development_en.pdf (Accessed November 1, 2023).

Guy, W., 1976. ECDEU Assessment Manual for Psychopharmacology, Revised. National Institute of Mental Health, Rockville, MD.

Hunter, N.L., O'Callaghan, K.M., Califf, R.M., 2015. Engaging patients across the spectrum of medical product development: view from the US Food and Drug Administration. JAMA 314, 2499–2500. https://doi.org/10.1001/jama.2015.15818.

Jolliffe, I.T., 2002. Principal Component Analysis, Second ed. Springer-Verlag New York, Inc., New York, NY.

Kane, J.M., Skuban, A., Ouyang, J., Hobart, M., Pfister, S., McQuade, R.D., Nyilas, M., Carson, W.H., Sanchez, R., Eriksson, H., 2015. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. Schizophr. Res. 164, 127–135. https://doi.org/10.1016/j.schres.2015.01.038.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276. https://doi.org/10.1093/schbul/13.2.261.

Kieffer, C.M., Miller, A.R., Chacko, B., Robertson, A.S., 2020. FDA reported use of patient experience data in 2018 drug approvals. Ther. Innov. Regul. Sci. 54, 709–716. https://doi.org/10.1007/s43441-019-00106-1.

Marder, S.R., Hakala, M.J., Josiassen, M.K., Zhang, P., Ouyang, J., Weiller, E., Weiss, C., Hobart, M., 2017. Brexpiprazole in patients with schizophrenia: overview of short- and long-term phase 3 controlled studies. Acta Neuropsychiatr. 29, 278–290. https://doi.org/10.1017/neu.2016.57.

Marder, S.R., Eriksson, H., Zhao, Y., Hobart, M., 2020. *Post hoc* analysis of a randomised, placebo-controlled, active-reference 6-week study of brexpiprazole in acute schizophrenia. Acta Neuropsychiatr. 32, 153–158. https://doi.org/10.1017/neu.2020.8.

McIntyre, R.S., Ismail, Z., Watling, C.P., Weiss, C., Meehan, S.R., Musingarimi, P., Thase, M.E., 2022. Patient-reported outcome measures for life engagement in mental health: a systematic review. J. Patient Rep. Outcomes 6, 62. https://doi.org/10.1186/s41687-022-00468-5.

McIntyre, R.S., Therrien, F., Ismail, Z., Meehan, S.R., Miguelez, M., Larsen, K.G., Chen, D., MacKenzie, E.M., Thase, M.E., 2023. Effects of adjunctive brexpiprazole on patient life engagement in major depressive disorder: *post hoc* analysis of Inventory of Depressive Symptomatology Self-Report data. J. Psychiatr. Res. 162, 71–78. https://doi.org/10.1016/j.jpsychires.2023.04.012.

Opler, M.G.A., Yavorsky, C., Daniel, D.G., 2017. Positive and Negative Syndrome Scale (PANSS) training: challenges, solutions, and future directions. Innov. Clin. Neurosci. 14, 77–81. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5788255/.

Purnine, D.M., Carey, K.B., Maisto, S.A., Carey, M.P., 2000. Assessing positive and negative symptoms in outpatients with schizophrenia and mood disorders. J. Nerv. Ment. Dis. 188, 653–661. https://doi.org/10.1097/00005053-200010000-00003.

R Core Team, 2022. R: a language and environment for statistical computing. https://www.R-project.org/ (Accessed November 1, 2023).

Rai, S.K., Yazdany, J., Fortin, P.R., Aviña-Zubieta, J.A., 2015. Approaches for estimating minimal clinically important differences in systemic lupus erythematosus. Arthritis Res. Ther. 17, 143. https://doi.org/10.1186/s13075-015-0658-6.

Scheier, M.F., Wrosch, C., Baum, A., Cohen, S., Martire, L.M., Matthews, K.A., Schulz, R., Zdaniuk, B., 2006. The Life Engagement Test: assessing purpose in life. J. Behav. Med. 29, 291–298. https://doi.org/10.1007/s10865-005-9044-1.

Tavakol, M., Dennick, R., 2011. Making sense of Cronbach's alpha. Int. J. Med. Educ. 2, 53–55. https://doi.org/10.5116/ijme.4dfb.8dfd.

Thase, M.E., Ismail, Z., Meehan, S.R., Weiss, C., Regnier, S.A., Larsen, K.G., McIntyre, R.S., 2023. Assessment of patient life engagement in major depressive disorder using items from the Inventory of Depressive Symptomatology Self-Report (IDS-SR). J. Psychiatr. Res. 161, 132–139. https://doi.org/10.1016/j.jpsychires.2023.02.008.

Therrien, F., Meehan, S.R., Weiss, C., Dine, J., Brown, T.M., MacKenzie, E.M., 2022. Exploring life engagement from the perspective of patients with major depressive disorder: a study using patient interviews. J. Patient Rep. Outcomes 6, 111. https://doi.org/10.1186/s41687-022-00517-z.

Therrien, F., Ward, C., Chokka, P., Habert, J., Ismail, Z., McIntyre, R.S., MacKenzie, E.M., 2024. Adjunctive brexpiprazole for patient life engagement in major depressive disorder: a Canadian, phase 4, open-label, interventional study. Can. J. Psychiatry 69, 513–523. https://doi.org/10.1177/07067437241233965.

Trompetter, H.R., Ten Klooster, P.M., Schreurs, K.M.G., Fledderus, M., Westerhof, G.J., Bohlmeijer, E.T., 2013. Measuring values and committed action with the Engaged Living Scale (ELS): psychometric evaluation in a nonclinical sample and a chronic pain sample. Psychol. Assess. 25, 1235–1246. https://doi.org/10.1037/a0033813.

Vita, A., Barlati, S., Deste, G., Nibbio, G., Penn, D.L., Pinkham, A.E., McIntyre, R.S., Harvey, P.D., 2023. Life engagement in people living with schizophrenia: predictors and correlates of patient life engagement in a large sample of people living in the community. Psychol. Med. 53, 7943–7952. https://doi.org/10.1017/s0033291723002106.

Weiss, C., Meehan, S.R., Brown, T.M., Gupta, C., Mørup, M.F., Thase, M.E., McIntyre, R.S., Ismail, Z., 2021. Effects of adjunctive brexpiprazole on calmness and life engagement in major depressive disorder: *post hoc* analysis of patient-reported outcomes from clinical trial exit interviews. J. Patient Rep. Outcomes 5, 128. https://doi.org/10.1186/s41687-021-00380-4.

Weldring, T., Smith, S.M.S., 2013. Patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs). Health. Serv. Insights 6, 61–68. https://doi.org/10.4137/hsi.S11093.