NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Early Value Assessment

MT589 Digitally Enabled Therapies for Adults with Anxiety Disorder

External Assessment Group Addendum

Produced by: Cedar

Date: 27/02/2023

Correspondence to: Cedar, Cardiff Medicentre, Heath Park, Cardiff CF14 4UJ

Contains confidential information: Yes

The EAG has prepared this addendum in response to requests from NICE following the MTAC meeting for the topic.

Key issues addressed in this addendum

NICE Query	**EAG Response**
Companies raised concerns that some evidence may have been missing for their technology.	The EAG has reviewed the company submissions to ensure no relevant evidence has been excluded inadvertently from the main report. • Evidence from 3 additional studies has been reviewed and summarised in the addendum. • Available details for one additional ongoing study are summarised in section 2. • For other studies where there was a question over eligibility of inclusion, but which the EAG consider should be excluded, they have been added to section 3 of the addendum.
Adverse events were a key discussion point for the committee	The EAG reviewed all included studies for adverse event data and included a table in the addendum

1. Additional Clinical Evidence

An additional 3 studies have been included in this addendum (table 1). A rating of Green indicates an element that meets the scope fully, amber meets the scope partially and red indicates does not meet the scope.

The additional studies cover generalised anxiety (1 study) and PTSD (2 studies) and report on a range of outcomes including clinical outcomes, acceptability and uptake. Results from the additional studies are reported in table 2 for generalised anxiety and table 3 for post-traumatic stress disorder.

Results for generalised anxiety ([redacted]) relate to SilverCloud and are in line with findings from other studies reporting [redacted]For PTSD both studies relate the use of Spring. One study (Lewis 2017) reports improvements across a range of measures for people using Spring with significant differences reported for those using Spring compared with people in the delayed treatment group. It should be noted that by week 22, when all patients in the delayed treatment group had crossed over and completed treatment, the differences between the groups was no longer significant.

One study (Simon 2021) explored the views of 10 NHS commissioners and managers in relation to the acceptability and implementation of internet-based therapies. Three key themes were identified including increasing acceptance of internet-based therapies, potential for offering a solution to capacity issues which create barriers to the provision of face to face therapy and the need for a national coordinate approach with appropriate training and supervision to facilitate roll-out. Although based on Spring which is used in for PTSD, the findings from this study may be generalisable across all technologies.

Table 1: Additional Studies

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAG comments
Spring				
Study: Lewis 2017 **Location:** UK	**Design:** exploratory single blind randomised trial **Aim:** to establish efficacy of guided internet-based self-help for PTSD in comparison to a delayed treatment control group. **Comparator:** Delayed Treatment (Waitlist until week 14 then crossover to treatment arm) **Therapist Involvement:** 1-hour face to face session at beginning with fortnightly 30min face to face or telephone sessions. Therapist guide also contacted participants by phone / e-mail between appointments **Amber**	**Participants:** N=42 adults who continued to meet diagnostic criteria for DSM-5 PTSD of mild to moderate severity after a 2-week period of symptom monitoring **Setting:** Traumatic Stress service, expanded to include mental health services at a primary care level **Green**	**Primary Outcome** CAPS-5 (30 item structured interview that corresponds to the DSM-5 criteria for PTSD) **Secondary Outcome** • PTSD checklist for DSM-5 • Beck Depression Inventory (BDI • Beck Anxiety Inventory (BAI) • Alcohol Use Disorders Identification Test (AUDIT) • Social Support Questionnaire (SSQ) • Sheehan Disability Scale (SDS) **Green**	Small number of participants and comparator not relevant to scope.
Study: Simon 2021	**Design:** Qualitative Interview Study	**Participants:** N= 10 individuals in NHS roles likely to fund, commission, signpost-to, or	Interview findings around issues such as capacity, acceptability and usability	Not clinical outcomes, limited evidence on the views of NHS

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAG comments
Location: UK	**Aim:** explore in-depth the views on Internet-based psychological therapies and their implementation from the perspective of NHS commissioners and managers. **Comparator:** N/A **Green**	implement an i-CBT intervention for NHS patients **Setting:** NHS **Green**	**Green**	professionals likely to use / recommend digital therapies.
SilverCloud				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2: Results for generalised anxiety

Study	Technology	Anxiety measures	WSAS	Recovery and remission	Acceptability and usage
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3: Results for PTSD

Study	Technology	PTSD specific measures: Change in CAPS-5, PCL-5 and PSS-I	Acceptability and usage	Therapist time
Lewis 2017	Spring	Clinician assessed traumatic stress symptoms: • Immediately after treatment (week 10) significantly lower levels of compared with delayed treatment group (Group mean difference of 18.60 points) • Similar differences at week 14 (group mean difference of 17.16) • At week 22 differences were not significant CAPS scores and PTSD checklist scores showed the greatest improvement from baseline to week 10 in the treatment group and from week 14 to week 22 in the delayed	19% of participants dropped out prematurely with reasons for dropping out including: • Perceived lack of time • Finding the program difficult • Feeling symptoms had improved sufficiently	Mean amount of therapist input was 147.53 mins per participant including a mean 3.09 face to face meetings, 2.09 telephone calls and 1.00 e-mails.

Study	Technology	PTSD specific measures: Change in CAPS-5, PCL-5 and PSS-I	Acceptability and usage	Therapist time
		treatment group. No significant difference observed between the groups at week 22. Similar patterns were observed across measures of depression, anxiety and functional impairment– no statistically significant differences once both groups received treatment		
Simon 2021	Spring		Three main themes identified: • Internet based therapies offer a solution to barriers to face to face therapies that result from capacity issues in the service • Acceptance of internet-based therapies is growing as they are accessible and empowering treatment options however reservations include potential threat to therapeutic relationship and risk they may exclude some individuals • Successful roll out of internet-based interventions should include a national approach to implementation with clear understanding of implementation requirements. Barriers to successful roll-out include set	

Study	Technology	PTSD specific measures: Change in CAPS-5, PCL-5 and PSS-I	Acceptability and usage	Therapist time
			up costs and delays due to NHS inflexibility.	

2. Ongoing Studies

One company (Cerina) provided a protocol for a trial using the technology for OCD which may provide evidence in the future. The feasibility trial aims to investigate the feasibility of the Cerina app (including participants` views on the quality and usability of the User Interface Design) and the clinical aspects of the Cerina application as well as testing the preliminary effects of the intervention in reducing OCD symptoms over time. There are no details for timelines and currently the study is not mentioned on the company website.

3. Adverse Events and Safety

The committee considered adverse events and safety of the technologies to be one of the most important factors. While the EAG identified no safety concerns with any of the technologies, the committee were concerned that safety in the context of this topic might include broader and relate specifically to factors such as mental health and well-being.

The EAG has revisited the included studies and reported on any potential adverse events and / or safety concerns for completeness (table 4). One study (Richards 2020) reported rates of deterioration as adverse events, however other studies have reported deterioration as a clinical outcome.

Table 4: Safety Adverse Events

Study	Adverse Event data collected	Adverse Events reported	Considered to be study / treatment related
Bisson 2022	Possible adverse events considered to be a deterioration in mental health assessed by outcome measures and suicidal ideation.	Risk assessment framework triggered 105 times, once due to report of self-harm and remaining for suicidal ideation. Six serious adverse events reported	No
Duffy 2020	No details – significant SAEs were handled by the clinical team and escalated appropriately	None reported	

Study	Adverse Event data collected	Adverse Events reported	Considered to be study / treatment related
Richards 2020	Rates of deterioration at post-treatment (increase in PHQ-9 ≥ 6 and/or GAD-7 ≥ 4) and an increase in the number of diagnoses at 3-months were considered as adverse events	5.2% (n=10) in the intervention arm and 12.2% (n=11) in the waitlist arm deteriorated. No severe adverse events reported 25.7% (n=55) in the intervention arm received further mental health treatment during follow-up	
Wilhelm 2020	Monitored by investigator at each clinical assessment	None reported	
Wilhelm 2022	A standardised adverse event form which consisted of 4 yes / no questions	30 out of 80 participants reported a total of 42 adverse events during the 12-week randomized controlled phase of the trial. • 45.2% were mild (new event that did not interfere with activities of daily living) • 47.6% were moderate (new event that posed some interference or required intervention to prevent interference) • 7.1% were severe (new event that posed interference and required intervention). Two adverse events (one in each group) resulted in an investigator-initiated study withdrawal; No serious adverse events occurred in this trial.	Adverse events were found to be definitely unrelated (69.1%) or unlikely to be related (30.9%)

4. Excluded Studies

Study	Technology	Reason for Exclusion
Beatty 2022	Wysa	The aim and outcomes of the study were not relevant to the scope.
Cheng 2022a	Wysa	Population is not within scope. People with chronic pain and symptoms of anxiety / depression.

Cheng 2002b	Wysa	Population is not within scope. Orthopaedic patients with symptoms of anxiety and depression.
Ingelsias 2022	Wysa	Not within scope. People using an adapted 'Return to Work' version of Wysa. The version of the technology is not commercially available.
Inkster 2022	Wysa	Population not within scope – people with self-reported maternal event while using Wysa.
Eilert 2022	SilverCloud	Outcomes were not considered to be within the scope of this review (use of CBT skills following completion of treatment)
Eilert 2022	SilverCloud	Outcomes were not considered to be within the scope of this review (follow-up on use of CBT skills following completion of treatment)
Enrique 2021	SilverCloud	Outcomes were not considered to be within the scope of this review (beliefs in rumination and emotion regulation and their impact on CBT use)
Lawler 2021	SilverCloud	N=15 Results for depression and anxiety cannot be separated
Grime 2004	Beating the Blues	Narrative Review
Van Den Berg 2004	Beating the Blues	Narrative Review
Hunt 2006	Beating the Blues	Depression is the primary descriptor
Learmonth & Rai 2007	Beating the Blues	Narrative Review
Mitchell & Dunn 2007	Beating the Blues	Narrative Review
Learmonth 2008	Beating the Blues	Depression appears to be the primary descriptor and results not reported separately for depression or anxiety
Rollman 2018	Beating the Blues	Not relevant to scope – study looks at including an internet support group as part of care is effective.
McMurchie 2013	Beating the Blues	Primary indication for use of technology is depression. Depression with co-morbid anxiety is included but EAG

		considered this not to be relevant to the anxiety topic.
Proudfoot 2004	Beating the Blues	Assessment made using GHQ
Pittaway 2010	Beating the Blues	Outcomes were not considered to be within the scope of this review. N=50 across 3 groups,
Thew 2022	iCT-SAD	N=44, compared with waitlist control and not a UK based study
Goessl 2017	Resony	Outcomes not relevant to scope – physical changes in factors such as heart rate variability, autonomic reactivity
Levine 2016	Resony	Outcomes not relevant to scope – physical changes in factors such as heart rate variability, autonomic reactivity
Shinba 2017	Resony	Outcomes not relevant to scope – physical changes in factors such as heart rate variability, autonomic reactivity
Chalmers 2014	Resony	Outcomes not relevant to scope – physical changes in factors such as heart rate variability, autonomic reactivity
Chang 2013	Resony	Outcomes not relevant to scope – physical changes in factors such as heart rate variability, autonomic reactivity
Fisher & Newman 2013	Resony	Outcomes not relevant to scope – physical changes in factors such as heart rate variability, autonomic reactivity
Chang 2013	Resony	Outcomes not relevant to scope – physical changes in factors such as heart rate variability, autonomic reactivity
Pittig 2013	Resony	Outcomes not relevant to scope – physical changes in factors such as heart rate variability, autonomic reactivity
Verma 2011	Resony	Outcomes not relevant to scope – physical changes in factors such as heart rate variability, autonomic reactivity
Conrad & Roth 2007	Resony	Outcomes not relevant to scope – physical changes in factors such as heart rate variability, autonomic reactivity

Francis & Pennebaker	Resony	Outcomes not relevant to scope – writing therapy
Lieberman	Resony	Outcomes not relevant to scope – writing therapy
Lewis 2013	Spring	Not relevant to scope – app / programme development study