Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

- Determine the quantity of evidence available for a technology of interest.
- Identify any gaps in the evidence.
- Inform decisions on topics that warrant fuller assessment by Health Technology Wales (HTW).

Topic exploration report number:	TER456
Topic:	Internet-based cognitive behavioural therapy for mild-to-moderate depression or anxiety in people with breast cancer and survivors of breast cancer
Summary of findings:	Internet-based cognitive behavioural therapy (iCBT) is a form of self-help for mental health issues and is delivered via digital methods such as computers or smartphones. It can be guided by a qualified health professional, or unguided.

Seven randomised controlled trials assessing iCBT were identified; four assessed people with breast cancer or survivors of breast cancer and three assessed various cancer types including those with, or treated for, breast cancer. There were mixed findings for the effect of iCBT on depression and anxiety symptoms and quality of life. Adherence to iCBT programmes tended to decrease throughout the treatment period. However, patient satisfaction generally ranked highly when reported.

There was heterogeneity in the type of iCBT programme used, follow-up times, measures used to assess depression or anxiety, the stage of cancer and type of cancer in the study participants. Most study participants were breast cancer survivors who had completed primary treatment. It was unclear whether all the participants had mild-to-moderate depression or anxiety, and whether the "treatment-as-usual" or "care-as-usual" study control groups are the same as standard of care in NHS Wales. We did not identify any economic evidence specifically relating to those with or treated for breast cancer, and there are uncertainties around the applicability of the economic analyses in National Institute for Health and Care Excellence (NICE) guidance and international health technology assessments. |

Introduction and aims

Depression refers to a wide range of mental health problems characterised by a loss of interest and enjoyment in ordinary things and experiences, low mood, and a range of associated emotional, cognitive, physical and behavioural symptoms (NICE 2022). Mild depression occurs when less than five symptoms exist, and they only result in minor functional impairment. Moderate depression describes symptoms of functional impairment that are between 'mild' and 'severe' (NICE 2022). Anxiety is a feeling of unease, such as worry or fear, that can be mild to severe (NHS 2022).

Cognitive behavioural therapy (CBT) is a talking therapy that can help people manage their problems by changing negative thought patterns and behaviours. Internet-based CBT (iCBT) is a digital way of providing this as a form of self-help using mobile phones or computers, and can be guided by a mental health professional or unguided. Internet-based CBT is sometimes referred to as computerised CBT (CCBT), but CCBT includes a wider range of interventions than the internet, such as CD-ROMs and DVDs (NICE 2009).

People with breast cancer and survivors of breast cancer may have symptoms of depression or anxiety, and iCBT aims to provide a more accessible resource to help manage these conditions. These people may currently be treated with a range of interventions, including physical activity programmes, peer support groups, self-help books, face-to-face CBT, and antidepressants (NICE 2009). Some of these people may also be on a waiting list for treatment. Internet-based CBT may allow for treatment to begin sooner than it otherwise would and for it to be done remotely, reducing the need to visit healthcare professionals.

Health Technology Wales received a submission for the new 'Space in Breast Cancer from Depression and Anxiety' programme from SilverCloud (Amwell), which is an iCBT platform used to support mental health via a variety of programmes that are already in use in all health boards in Wales. We searched for evidence on the clinical and cost-effectiveness of iCBT, including but not limited to SilverCloud, for people with, and survivors of, breast cancer with mild-to-moderate depression or anxiety when compared with standard of care.

Evidence overview

The technologies for providing iCBT are digital health technologies, determined to be Tier C technologies according to the [Evidence Standards Framework for Digital Health Technologies](#) developed by the National Institute for Health and Care Excellence (NICE). Technologies within this classification are used to treat a condition. In these cases, information provided by the digital technology will be used to take an immediate or near-term action to treat, prevent, or mitigate by means of providing therapy to a human body. For technologies of this classification, it is recommended that evidence should include one or more high-quality interventional studies to support the claimed benefits of the digital health technology in a relevant setting, showing improvements in relevant outcomes. Randomised controlled trials (RCTs) are preferable, but high-quality, comparative real-world study designs may also be acceptable.

Guidance and Standards

No guidance or standards were identified specifically addressing iCBT for depression or anxiety in people with, or survivors of, breast cancer.

However, NICE Clinical guideline 91 (CG91) (2009) for depression in adults with chronic physical health problems, which includes cancer, states that CCBT should be considered for patients with

persistent subthreshold depressive symptoms or mild to moderate depression and a chronic physical health problem, and for patients with subthreshold depressive symptoms that complicate the care of the chronic physical health problem. The NICE criteria for CCBT are detailed below:

"iCBT should be provided via a stand-alone computer-based or web-based programme; include an explanation of the CBT model, encourage tasks between sessions, and use thought-challenging and active monitoring of behaviour, thought patterns and outcomes; be supported by a trained practitioner, who typically provides limited facilitation of the programme and reviews progress and outcome; typically takes place over nine to twelve weeks, including follow up".

NICE CG91 included a research recommendation to use a RCT of at least 18-months duration to investigate the efficacy of counselling compared with low-intensity cognitive and behavioural interventions (including CCBT) and treatment-as-usual in the treatment of depression in patients with a chronic physical health problem (NICE 2009).

NICE guideline 222 (NG222), for treatment of a new episode of depression in adults, included a network meta-analysis and recommended CCBT as a first-line treatment option (within the class of guided self-help) for subthreshold, mild, moderate and severe depression. Unguided self-help was not recommended (NICE 2022). This guideline is not specific to people with depression or anxiety and co-existing conditions (NICE 2022).

NICE have published early value assessments (EVAs) for digitally enabled therapies for adults with anxiety disorders and depression, respectively (NICE 2023a, NICE 2023b). Several digitally enabled therapies were recommended for use whilst further evidence is generated: six for adults with anxiety disorders and three for adults with depression. Both EVAs make several research recommendations for generating more evidence on various outcomes relating to clinical effectiveness, adverse events, and health-related quality of life. The recommended technologies for anxiety are: Beating the Blues (365 Health Solutions) and Space from Anxiety (SilverCloud) for generalised anxiety symptoms or unspecified anxiety disorder, iCT-PTSD (OxCADAT) and Spring (Cardiff University) for post-traumatic stress disorder, iCT-SAD (OxCADAT) for social anxiety disorder, and Perspectives (Koa Health) for body dysmorphic disorder. The technologies for anxiety are dependent on various regulatory approvals and assessment by NHS England Talking Therapies. The recommended technologies for depression are: Beating the Blues (365 Health Solutions), Deprexis (Ethypharm Digital Therapy), and Space from Depression (SilverCloud).

A health technology assessment (HTA) by the Norwegian Institute of Public Health (2018) concluded that iCBT with the support of a therapist reduces anxiety and depression, and improves quality of life in adults compared to no treatment. Internet-based CBT, with and without therapist support, reduced symptoms of depression and anxiety more than face-to-face CBT (Norwegian Institute of Public Health 2018). The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) (2021) found that iCBT is equivalent to group CBT for adults with social anxiety, and equivalent to face-to-face individual CBT for health anxiety. It was also found that iCBT in addition to usual treatment for depression in adults may further reduce symptoms in the short term. It is unclear whether the studies in these HTAs included people with breast cancer or breast cancer survivors, and the included studies were mainly reported as being of low certainty.

Individual studies

Seven RCTs were identified that investigated iCBT for people with cancer or cancer survivors. Four of the seven studies looked specifically at breast cancer survivors (Akechi et al. 2023, Akkol-Solakoglu and Hevey 2023, Holtdirk et al. 2021, Wagner et al. 2021). The remaining three RCTs included people

with different types of cancer who may still be undergoing primary treatment, including those with breast cancer (Børøsund et al. 2020, Hauffman et al. 2020, Murphy et al. 2020). All but one study used "treatment-as-usual" or "care-as-usual" as the control; Wagner et al. (2021) used an attention control of health management content delivered via an eHealth platform, but it is uncertain whether this may be part of standard of care in NHS Wales. In addition, we identified a non-comparative pilot study investigating iCBT specifically for people with advanced cancer and depression or anxiety, of which 56% had breast cancer (Murphy et al. 2021).

Various scales for measuring depression and anxiety were used, and the effect of iCBT compared to controls was variable. Internet-based CBT was found to significantly improve depression symptoms by Akechi et al. (2023), Akkol-Solakoglu and Hevey (2023), Hauffman et al. (2020), Holtdirk et al. (2021), Murphy et al. (2020), Wagner et al. (2021). However, Hauffman et al. (2020) stated that the difference was statistically but not clinically significant. Anxiety symptoms were significantly improved with iCBT compared to controls in two studies (Akkol-Solakoglu and Hevey 2023, Murphy et al. 2020), whilst four found no significant improvement (Akechi et al. 2023, Børøsund et al. 2020, Hauffman et al. 2020, Holtdirk et al. 2021). In the non-comparative pilot study, there were significant improvements in depression and anxiety symptoms, using the Hospital Anxiety and Depression Scale, both at post-intervention and three-months follow-up compared to baseline in adults with advanced cancer (Murphy et al. 2021).

Quality of life was also measured using various surveys and produced variable results. One study found that iCBT led to greater improvements in quality of life than treatment-as-usual (Holtdirk et al. 2021), whereas two others found no significant difference (Akkol-Solakoglu and Hevey 2023, Hauffman et al. 2020). Four out of eight domains of the SF-36-Item Short-Form Health Survey (RAND-36 version) significantly improved with iCBT compared to treatment-as-usual (Børøsund et al. 2020).

Adherence to iCBT programmes tended to decrease throughout the treatment period. Numbers of participants completing at least one lesson ranged from 75 to 89% (Akechi et al. 2023, Akkol-Solakoglu and Hevey 2023, Wagner et al. 2021), whereas full completion rates ranged from 51 to 58% (Akkol-Solakoglu and Hevey 2023, Børøsund et al. 2020, Wagner et al. 2021). In a two-step study by Hauffman et al. (2020), only 20% of participants offered iCBT in the study's second step accepted it. However, patient satisfaction generally ranked highly when reported (Børøsund et al. 2020, Holtdirk et al. 2021, Murphy et al. 2020). The use of tele-coaching led to greater adherence and lower dropout rates compared to without it (Wagner et al. 2021).

The non-comparative pilot study, investigating iCBT specifically for people with advanced cancer and depression or anxiety, found that progression of the disease affected adherence, with only 46% of the progression subgroup completing five-to-six out of the six lessons compared to 71% of the stable subgroup (Murphy et al. 2021).

Economic evidence

No economic studies specifically for iCBT in people with breast cancer or breast cancer survivors were identified. However, the guidelines discussed above included economic analyses.

NICE CG91 (NICE 2009) included a previous economic analysis by Kaltenhaler et al. (2006), which compared CCBT courses with treatment-as-usual. Three CCBT courses were considered in the analysis; 'Beating the Blues', 'Overcoming Depression' and 'Cope'. All CCBT courses were found to be more effective and more costly than treatment-as-usual. All had incremental cost-effectiveness ratios (ICER) below a threshold of £20,000 per quality adjusted life-year (QALY), indicating that all CCBT courses were cost effective in comparison to treatment-as-usual. 'Beating the Blues' had the

lowest ICER in comparison to treatment-as-usual (£1,801 per QALY) and was the only package evaluated within the context of an RCT. However, it is unclear whether any of the participants in the RCT used to inform this economic analysis had cancer.

Economic modelling in NG222 (2022) evaluated the cost effectiveness of pharmacological, psychological and physical interventions for the treatment of a new episode of 'less severe depression' and 'more severe depression' in adults treated in primary care. Less severe depression was defined as subthreshold and mild depression, while more severe depression was defined as moderate and severe depression. The interventions considered in the analysis were determined by the availability of effectiveness data from a network meta-analysis (NMA), which was conducted to inform this guideline. The results provide rankings of treatments based on the cost effectiveness results. In people with less severe depression, CBT was found to be the preferred strategy. CCBT and CCBT with support were ranked as the 6th and 8th preferred strategies (of 16 strategies). In people with more severe depression, individual problem solving was found to be the preferred strategy. CCBT with support and CCBT were found to be the 11th and 16th preferred strategies (of 20 strategies). However, this economic analysis was also not specific to the breast cancer population and applicability cannot be certain.

Further economic modelling in the EVA for anxiety found that digitally enabled therapies could be cost-effective when compared to standard care in NHS England's Talking Therapies (NICE 2023a). The results suggest that Beating the Blues, Deprexis and Space from Depression could be cost-effective for less severe depression (NICE 2023b). Only Deprexis could be modelled for more severe depression and the results suggest that it could be cost-effective as well as generic CCBT. However, these technologies are less likely to be the most cost-effective options when compared to standard care for depression.

The Norwegian Institute of Public Health's HTA (2018) includes a cost-minimisation analysis comparing guided iCBT to conventional face-to-face CBT. They found that direct costs associated with iCBT are comparable to direct treatment costs for conventional face-to-face therapy. SBU (2021) states that iCBT could be cost-saving for adults with social anxiety but could not assess cost effectiveness for depression due to a lack of evidence on longer-term effects.

Ongoing research

A meta-analysis of the effect of iCBT on quality of life for breast cancer survivors is registered on PROSPERO (Mingyue et al. 2021). However, an estimated completion date of August 2021 has been given but we were unable to find the publication.

It is not certain if a comparative study is intended to follow the pilot study, of iCBT for people with advanced cancer, previously described by Murphy et al. (2021).

Areas of uncertainty

There are different types of iCBT programmes, and they are often developed to manage a specific condition or symptom. This leads to differences between the interventions used in studies and it is uncertain how well these can be compared or grouped together.

Many studies used "treatment-as-usual" or "care-as-usual" as the control group but it is unclear what this involves, whether they are similar across studies, and how they compare to standard care in NHS Wales. It is unclear whether the studies we identified address the research recommendation

in NICE CG91 (2009), to investigate the efficacy of counselling compared with low-intensity cognitive and behavioural interventions and treatment-as-usual.

There was heterogeneity between the study participants. Whilst most studies included survivors of breast cancer, some included those with active disease undergoing treatment. We only identified one non-comparative study investigating iCBT in people with advanced cancer. Some of the studies included people with various forms of cancer and, whilst they often included a large proportion with breast cancer, results were not reported separately for these different types of cancer.

Some studies did not report the baseline depression or anxiety level of participants, meaning it was not always possible to determine whether it was mild-to-moderate.

There was heterogeneity in the follow-up times used in the studies, and no data were identified for follow-up times longer than ten months. There was also variation in the measurement surveys and scales used for depression and anxiety, with most using the Hospital Anxiety and Depression Scale (HADS), and it is unclear whether they are all used in NHS Wales. One study used the PHQ-9 and GAD-7 scales, which were highlighted as being used in at least one health board in Wales.

We did not identify any economic evidence specifically for iCBT in people with breast cancer or breast cancer survivors, and it is unclear whether the economic analyses identified in the NICE guidance or international HTAs are applicable to this population.

Literature search results

Health technology assessments and guidance

NICE. (2009). Depression in adults with a chronic physical health problem: recognition and management. Clinical guideline CG91. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/cg91 [Accessed 09 Mar 2023].

NICE. (2022). Depression in adults: treatment and management. Guideline NG222. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ng222 [Accessed 14 Mar 2023].

NICE. (2023a). Digitally enabled therapies for adults with anxiety disorders: early value assessment. Early value assessment HTE9. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/hte9 [Accessed 16 May 2023].

NICE. (2023b). Digitally enabled therapies for adults with depression: early value assessment. Early value assessment HTE8. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/hte8 [Accessed 16 May 2023].

Norwegian Institute of Public Health. (2018). Therapist-supported internet therapy for mental disorders – a health technology assessment. Health technology assessment. Norwegian Institute of Public Health. Available at: https://www.fhi.no/en/publ/2018/Therapist-supported-internet-therapy-for-mental-disorders/ [Accessed 16 Mar 2023].

Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU). (2021). Internet-based psychological treatment for anxiety and depression. SBU Report No. 337. Swedish Agency for Health Technology Assessment and Assessment of Social Services. Available at: https://www.sbu.se/337 [Accessed 09 Mar 2023].

None of these guidelines or HTAs are specific to breast cancer and, therefore, their applicability is uncertain.

Evidence reviews and economic evaluations

Kaltenthaler E, Brazier J, De Nigris E, et al. (2006). Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation. Health technology assessment (Winchester, England). 10(33): iii, xi-xiv, 1-168. doi: https://doi.org/10.3310/hta10330

Individual studies

Akechi T, Yamaguchi T, Uchida M, et al. (2023). Smartphone Psychotherapy Reduces Fear of Cancer Recurrence Among Breast Cancer Survivors: A Fully Decentralized Randomized Controlled Clinical Trial (J-SUPPORT 1703 Study). J Clin Oncol. 41(5): 1069-78. doi: https://doi.org/10.1200/jco.22.00699

Akkol-Solakoglu S, Hevey D. (2023). Internet-delivered cognitive behavioural therapy for depression and anxiety in breast cancer survivors: Results from a randomised controlled trial. Psycho-Oncology. 32(3): 446-56. doi: https://doi.org/10.1002/pon.6097

Børøsund E, Ehlers SL, Varsi C, et al. (2020). Results from a randomized controlled trial testing StressProffen; an application-based stress-management intervention for cancer survivors. Cancer Med. 9(11): 3775-85. doi: https://doi.org/10.1002/cam4.3000

Hauffman A, Alfonsson S, Bill-Axelson A, et al. (2020). Cocreated internet-based stepped care for individuals with cancer and concurrent symptoms of anxiety and depression: Results from the U-CARE AdultCan randomized controlled trial. Psycho-Oncology. 29(12): 2012-8. doi: https://doi.org/10.1002/pon.5489

Holtdirk F, Mehnert A, Weiss M, et al. (2021). Results of the Optimune trial: A randomized controlled trial evaluating a novel Internet intervention for breast cancer survivors. PLoS One. 16(5): e0251276. doi: https://doi.org/10.1371/journal.pone.0251276

Murphy MJ, Newby JM, Butow P, et al. (2020). Randomised controlled trial of internet-delivered cognitive behaviour therapy for clinical depression and/or anxiety in cancer survivors (iCanADAPT Early). Psycho-Oncology. 29(1): 76-85. doi: https://doi.org/10.1002/pon.5267

Murphy MJ, Newby JM, Butow P, et al. (2021). A mixed methods pilot and feasibility open trial of internet-delivered cognitive behaviour therapy (iCanADAPT Advanced) for people with advanced cancer with depression and/or anxiety. Internet Interventions. 26: 100449. doi: https://doi.org/10.1016/j.invent.2021.100449

Wagner LI, Tooze JA, Hall DL, et al. (2021). Targeted eHealth Intervention to Reduce Breast Cancer Survivors' Fear of Recurrence: Results From the FoRtitude Randomized Trial. J Natl Cancer Inst. 113(11): 1495-505. doi: https://doi.org/10.1093/jnci/djab100

Studies with an intervention arm of iCBT specifically for insomnia or menopausal symptoms were excluded as the primary condition for therapy was not anxiety or depression and the effect on these symptoms may not be direct due to co-morbidities.

Ongoing research

Mingyue P, Jiaxin Z, Haiqun H, et al. (2021). The effect of internet-based cognitive behavioral therapy on the quality of life of breast cancer survivors: a meta-analysis. PROSPERO. Available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021264105 [Accessed 13 Mar 2023].

Date of search:	March 2023
Concepts used:	Cognitive behavio(u)ral therapy, CBT, internet-based CBT, internet-delivered CBT, iCBT, computerised CBT, CCBT, SilverCloud, breast cancer

Proposed research question and evidence selection criteria (if selected)

Proposed research question	What is the clinical and cost effectiveness of internet-based cognitive behavioural therapy for mild-to-moderate depression or anxiety in people with breast cancer and survivors of breast cancer compared to standard care?

	Included	**Excluded**
Population	People with breast cancer, or survivors of breast cancer, with mild-to-moderate depression or anxiety	Severe depression
Intervention	Guided internet-based cognitive behavioural therapy for mild-to-moderate depression or anxiety	Cognitive behavioural therapy in tandem with other psychosocial interventions or face-to-face interventions Cognitive behavioural therapy for insomnia or menopausal symptoms
Comparison/ comparators	Treatment-as-usual, including: Face-to-face CBT Other forms of CBT and self-help, such as books Waiting list Physical activity programmes Peer support groups Antidepressants	
Outcomes	Depression scores using appropriate surveys Anxiety scores using appropriate surveys Quality of life Adherence Patient satisfaction Resource use	
Study design	We will include the following clinical evidence in order of priority: • Systematic reviews • Randomised or non-randomised trials. • Non-randomised trials. We will only include evidence for "lower priority" evidence where outcomes are not reported by a "higher priority" source. We will also search for economic evaluations or original research that can form the basis of an assessment of costs/cost comparison.	