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eHealth interventions for anxiety and depression in children and adolescents with long-term physical conditions (Protocol)

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[Intervention Protocol]

eHealth interventions for anxiety and depression in children and adolescents with long-term physical conditions

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of eHealth interventions in comparison with controls (treatment as usual, waiting list, attention placebo, psychological placebo or non-psychological treatment) for treating anxiety and depression in children and adolescents with long-term physical conditions.

BACKGROUND

Description of the condition

Long-term conditions or chronic illnesses of childhood are variably defined in the literature, but usually includes physical, psychological or cognitive problems lasting more than three months, which impair functioning (Van der Lee 2007). It is estimated that 10% to 12% of children internationally are affected by long-term physical conditions (Eiser 1997). Asthma is the most common long-term physical condition of childhood, followed by diabetes and epilepsy (Burkart 2002). Less common long-term physical conditions include respiratory conditions such as cystic fibrosis and bronchiectasis, cardiovascular conditions such as congenital heart disease, gastrointestinal conditions such as Crohn's disease, renal conditions such as chronic kidney disease, neurological conditions such as muscular dystrophy, chronic pain, cancer and others (Burkart 2002). The prevalence of long-term conditions is now greater than acute illness in some developed countries (Halfon 2010). Epidemiological studies show that the risk of psychological difficulties, particularly anxiety and depression, is substantially increased in children and adolescents with long-term physical conditions (Pless 1971; Cadman 1987; Gortmaker 1990; Newacheck 1991; Weiland 1992; Wallander 1995; Opolski 2005).

Anxiety disorders are common, occurring in 2.6% to 5.2% of children under 12 years and 5% to 19% of all children and adolescents (Costello 2004). The presentation of anxiety disorders varies with age, from separation anxiety, undifferentiated worries and somatic complaints in younger children, to specific phobias, panic disorder and social anxiety in older children and adolescents. Childhood anxiety disorders often persist into adolescence (Last 1996) and

early adulthood (Last 1997), and yet they often remain untreated or diagnosed late (Schneier 1992). Anxiety disorders are associated with poor academic performance, and personal and social dysfunction (Pine 2009). They may also be comorbid with depression (Kovacs 1989), substance abuse (Kushner 1990), attention-deficit/hyperactivity disorder (ADHD), and conduct disorder (Bittner 2007), and are associated with suicidal behaviours and death by suicide (Hill 2011). Anxiety has been identified in children and young people with long-term physical conditions as an area of clinical significance (Benton 2007; Pao 2011). It may arise from a number of different mechanisms including confrontation by dangerous stimuli such as threatening symptoms of illness or distressing procedures and unpredictable events, increased fear of death in life-threatening diseases, having a reduced sense of control over one's circumstances, experiencing peer rejection or parental overprotection and experiencing illness-specific symptoms such as shortness of breath in asthma (Lewis 2003; Pinquart 2011). Risk factors for developing anxiety in people with long-term conditions include younger age, female gender and type of illness (Hermanns 2005).

Depression is another common, yet under-recognised, problem with an overall prevalence of 0.4% to 2.5% in primary school children, and from 0.4% to 8.3% in adolescents (Birmaher 1996a). A 30-year study of American children indicated a depression rate of 2.8% in children under the age of 13 years and 5.6% in young people aged 13 to 18 years (Costello 2004). Rates rise rapidly during adolescence (Feehan 1993; Fergusson 1993; Feehan 1994; Fergusson 2001). By the age of 19 years, between one fifth and a quarter of young people have suffered from a depressive disorder (Lewinsohn 1993; Lewinsohn 1998). Depression is associated with poor academic performance, social dysfunction, substance abuse, and attempted and completed suicide (Brent 1986; Fleming 1993; Rhode 1994; Rao 1995; Birmaher 1996a; Birmaher 1996b; Brent 2002). Even subthreshold depression is associated with an increased risk of depression (Gonzalez-Tejera 2005), substance abuse (Judd 2002), suicidal behaviour (Fergusson 2006) and mortality (Cuijpers 2002). Depression may be comorbid with anxiety in 15.9% to 61.9% of children identified as either anxious or depressed, and measures of anxiety and depression are highly correlated (Brady 1992). Depression has also been identified as occurring more commonly in children and adolescents with long-term physical conditions (Dantzer 2003; Pinquart 2011). Depressive symptoms have been reported in as many as 40% of children with a long-term condition and socialisation problems (Denny 2014). Risk factors for depression in long-term conditions are thought to include low self-esteem and negative attributional style (Burke 1999).

Description of the intervention

Psychological interventions are defined as any psychotherapeutic treatment (talking therapy) specifically designed to change cognition or behaviour, or both, with the intention of improving outcomes (Eccleston 2012). Evidence regarding interventions for psychological problems in children with long-term physical conditions is limited (Compas 2012). The majority of interventions specifically designed for children and adolescents with long-term physical conditions focus on compliance with medical treatment, education about the medical condition and improving aspects of medical care (Smith 1986; Fielding 1999). Psychological issues, especially anxiety and depression, are usually addressed using standard psychological treatments which may or may not have been tested in this population. Access to such therapies may be limited depending upon the availability of community child and adolescent mental health services, paediatric consultation liaison services and other community-based health services.

eHealth is an emerging and fast-developing field of research and practice that involves the application of digital technologies to support or deliver health interventions. eHealth programs have many advantages: the fidelity of the intervention process is embedded in the program; patients can access treatment at their convenience; and they can work at their own pace in privacy. Computers may be preferable for some who are unable (e.g. those living in rural areas) or reluctant (e.g. many adolescents) to seek traditional face-to-face care (Fleming 2015). eHealth interventions can take various forms: from reasonably simple, predominantly text-based programs (e.g. websites offering information), through multimedia and interactive programs that can incorporate emails or text messages, all the way to sophisticated applications such as virtual reality systems (e.g. used as a distraction to reduce pain in children) (Law 2011). They may also include serious games (Fleming 2015), and biofeedback programs that use galvanic skin response and heart variability sensors to detect stress-related physiological changes, e.g. used for stress management (Pop-Jordanova 2010) or relaxation training (Amon 2008).

Given the greater likelihood of psychological issues in children and adolescents with long-term physical conditions, and the increasing availability of eHealth technology, it is pertinent to consider the value of eHealth-based psychological therapies/interventions in addressing these conditions, whether the computer programs are of generic design or specifically designed for this population. A growing body of evidence suggests that computer-delivered interventions are feasible and potentially efficacious in delivering compliance- and treatment-related behavioural therapies to children and adolescents with long-term physical conditions and their families (Stinson 2009). Furthermore, a review of 15 studies has suggested that children with chronic health conditions may be less likely to drop out from computerised interventions than from face-to-face interventions (Dunn 2011). The UK's National Institute for Health and Care Excellence (NICE) endorsed computerised interventions (based on cognitive behavioural therapy (CBT)) as the preferred first line of treatment for mild to moderate depression and anxiety (NICE 2006). There is limited evidence that computerised CBT may be useful for treating depression in

adults with long-term physical conditions (Sharp 2014). Whether or not this is the same for children and adolescents with long-term physical conditions remains to be determined, as does the effectiveness of other models of computerised psychotherapy with this population.

How the intervention might work

The aetiologies of both anxiety and depression are complex and include biological, psychological and social factors (Lewinsohn 1994; Cicchetti 1998; Goodyer 2000; McCauley 2001; Davidson 2002). Although modalities such as behaviour therapies (Martell 2001), third wave CBTs (Hayes 2004), psychodynamic therapies (McQueen 2008), humanistic therapies, integrative therapies (Mufson 2004) and systemic therapies (Carr 2006) may all be used to treat these conditions in face-to-face settings, we anticipate that the majority of eHealth interventions designed to address anxiety and depression are likely to be based upon the principles of CBT and to include an element of education about the psychological problem being addressed. Potential mechanisms for the main categories of psychological therapies are as follows.

Behaviour therapies aim to constructively change patients' behaviour towards their symptoms using operant conditioning. Common components used to treat anxiety and depression include psycho-education (Guerney 1971), relaxation training (Lowe 2002) and behavioural activation (BA) (Jacobsen 1996; Martell 2001). Biofeedback techniques may also be used (Schwartz 2003). CBT helps to link thoughts, feelings and behaviour, and target the situations or triggers that generate emotional responses. Cognitive appraisal of triggers and altering cognitions in order to change mood and behaviour are supported. CBT for depression is based on the cognitive model of depression (Beck 1976) which proposed that individuals prone to depression have cognitive distortions which result in a negative view of themselves, the world and the future. People with pessimistic "attribution styles" (Abramson 1978) have a bias toward viewing negative events as stable and self-induced versus positive events as transient and out of their control. This leads to a state of "learned helplessness" (Seligman 1979; Petersen 1993) and helplessness, as well as passivity in the face of challenges (McCauley 2001). CBT for depression in children and adolescents involves helping the child to: (1) recognise and evaluate their thoughts and identify different levels of mood in themselves, (2) recognise thoughts and behaviours that have contributed to his mood, (3) develop coping strategies to address them via effective problem-solving, and (4) evaluate outcomes. CBT has been shown to improve depression in children and adolescents (Harrington 1998; Reinecke 1998, Weisz 2006) and prevent relapse (Paykel 1999), although long-term results in studies have contradictory findings (Fonagy 2005). CBT for anxiety is based on Beck's cognitive model of anxiety which proposes that fear and anxiety are learnt responses that can be 'unlearnt'. CBT for anxiety in children and adolescents involves helping the child to: (1) recognise anxious feelings and bodily reactions, (2) clarify thoughts or cognitions in anxiety-provoking situations, (3) develop effective coping skills via modified self-talk, modelling, reality or in vivo exposure (Silverman 1996), role playing and relaxation training, and (4) evaluate outcomes. An element of treatment known as systematic desensitisation involves pairing anxiety stimuli, in vivo or by imagination, in a gradually-increasing hierarchy with competing relaxing stimuli such as pleasant images and muscle relaxation (James 2013). Recent advances have identified optimal methods of delivering exposure work including deepened extinction, variability and affect labelling (Craske 2014).

Third wave CBTs include acceptance and commitment therapy (ACT) (Hayes 1999; Hayes 2004), compassionate mind training (CMT), also known as compassion-focused therapy (Gilbert 2005; Gilbert 2009), functional analytic psychotherapy (FAP) (Kohlenberg 1991), metacognitive therapy for depression (Wells 2008; Wells 2009) and dialectical behaviour therapy (Linehan 1993; Koons 2001). These approaches use a combination of cognitive, behavioural and mindfulness techniques to assist people to manage situations without thought suppression or experiential avoidance (Hoffman 2008).

Psychodynamic therapies aim to resolve internal conflicts stemming from difficulties in past relationships and experiences (for example, sexual abuse). Such conflicts are thought to cause anxiety or psychic pain and are 'repressed' into the unconscious through the use of defence mechanisms (Bateman 2000). Although some defence mechanisms are adaptive, some are developmentally immature and can cause harm. Psychoanalytic (sometimes called psychodynamic) psychotherapy attempts to explore, through talking, play (with younger children) and the formation of a therapeutic relationship, how earlier experiences influence and perhaps seriously distort current thoughts, feelings, behaviours (actions) and relationships (McQueen 2008).

Humanistic therapies include grief therapy, supportive therapy and transactional analysis. These therapies are based on the premise that people are 'self-actualising', that is, they have an inherent tendency to develop their potential (Rogers 1951; Maslow 1970) and that they are self-aware, free to choose how they live, are responsible for the choices they make. Individualised rather than manualised or prescribed methods are undertaken to help them address their situation (Cain 2002).

Integrative therapies include interpersonal therapy (IPT) which addresses interpersonal conflict, difficulty with role transitions and experiences of loss, all of which are well-known risk factors in the development of depressive disorders in young people (Lewinsohn 1994; Birmaher 1996a; McCauley 2001). IPT has been proposed to work by activating several interpersonal change mechanisms including: (1) enhancing social support, (2) decreasing interpersonal stress, (3) facilitating emotional processing, and (4) improving interpersonal skills (Lipsitz 2013). It has been proven to be effective in the treatment of teenage depression (Mufson 1996; Mufson 2004; Bolton 2007).

Systemic therapies include family therapy, which is based on the premise that family members can influence one another's well-being and have a significant effect on both the development of symptoms and the outcomes of interventions (Carr 2006). There are a number of forms of family therapy including structural family therapy (Liebman 1974; Minuchin 1978) which centres on individual physiological vulnerability, dysfunctional transactional styles, and the role the sick child plays in facilitating conflict avoidance. Systems therapy, including Milan and post-Milan family therapy, attempts to elicit changes in the family dynamic by presenting information that encourages family members to reflect on their own behaviour within the family dynamic (Selvini 1978). Strategic family therapy acknowledges the effect of the illness on all family members and focuses on inducing change in symptoms by highlighting paradoxical intentions of family members (Madanes 1981). Attachment-based family therapy (ABFT) has been shown to be better than waitlist control for treating depression, and to lead to faster resolution of depressive symptoms and less suicidal ideation than waitlist control (Diamond 2002). ABFT has also been shown to lead to greater client and family satisfaction and retention when combined with CBT than when CBT is used alone for treating anxiety in young people (Siqueland 2005).

Why it is important to do this review

As the field of eHealth is a relatively new one, the evidence base regarding the effectiveness of eHealth interventions, especially in a population such as people with long-term conditions, is currently limited. This review aims to fill a gap in the literature by identifying and evaluating randomised controlled trials (RCTs) of eHealth-based interventions that directly or indirectly address anxiety or depression in children and adolescents with long-term physical conditions. Establishing this evidence base will inform the clinical use of existing effective resources and guide the development of newer and potentially more cost-effective and globally dispersible forms of treatment for this growing population.

Due to the unique qualities of eHealth interventions and the rapidly growing nature of this new field of health, eHealth interventions for addressing anxiety and depression in children and adolescents with long-term physical conditions are being considered separately from non-eHealth interventions by the same authors in a related review (Clarke 2016). This review also sits alongside a review of serious games for treating depression in children and adolescents who do not have a long-term condition (Fleming 2015). A few existing Cochrane reviews have already investigated the value of psychological therapies for anxiety and depression in adults (Barak 2008) and in children and adolescents. Of the latter, one review has addressed the prevention of depression in children and adolescents without addressing those with long-term conditions (Cox 2014). Two reviews have addressed the treatment of depression (Merry 2011) and anxiety (James 2013) in children and adolescents, but again not in those with long-term conditions. Two reviews have addressed psychological interventions for depression in adolescents who have a single condition such as congenital heart disease or pain (Lane 2013; Eccleston 2014) and one review has focussed on interventions for parents rather than children (Eccleston 2012).

OBJECTIVES

To assess the effects of eHealth interventions in comparison with controls (treatment as usual, waiting list, attention placebo, psychological placebo or non-psychological treatment) for treating anxiety and depression in children and adolescents with long-term physical conditions.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised controlled trials (RCTs) and cluster-randomised trials. Cross-over trials will also be included, though we will only use data from the first phase in order to avoid carry-over effects. We will exclude observational studies, quasi-randomised trials and non-randomised trials. We will not exclude any study on the basis of language of publication or publication status.

Types of participants

Age

We will include trials involving children and adolescents aged 0 to 18 years (or at least 80% of the sample within this age range).

Diagnosis

We will include studies whose participants have any single or mixed long-term physical condition of more than three-months' duration, and who have depression/subthreshold depression and/or anxiety. Depressive and anxiety disorders can be reliably diagnosed through structured clinical interviews and symptom severity may be assessed by either patient- or clinician-administered validated rating scales (Sadock 2005) based on DSM III, IV or 5 (American Psychological Association 2013) or ICD 9 or 10 (World Health Organization 1992) criteria.

Comorbidities

Those with any mixed long-term conditions and with both anxiety and depression will be included; we will include studies of those who may also have any other type of comorbid physical (e.g. asthma, diabetes, epilepsy) or mental health condition (e.g. attention deficit and hyperactivity disorder, obsessive compulsive disorder, schizophrenia).

Setting

We will include studies involving those treated in hospital and community settings.

Types of interventions

Experimental intervention

Experimental interventions will include any eHealth intervention that has measured changes in anxiety or depression and that has been tested in children and adolescents with long-term conditions. These may be delivered via the Internet (e.g. static or interactive websites, automated emails or web-based applications), cellular phones (e.g. automated phone calls or short text messages) or smart phones (e.g. mobile websites or smart phone applications). They may be entirely individually utilised (self-help) or therapist-supported and may include parent participation, but not "telemental health" where psychological intervention is provided remotely, via telephone, chatroom, email or videoconferencing and not interventions that are designed only for parents. Eligible modalities of therapy will include the following.

1. Cognitive behavioural therapy (CBT) (Harrington 1998; Reinecke 1998; Weisz 2006).
2. Behaviour therapies (e.g. relaxation training) (Lowe 2002)).
3. Third wave CBTs (e.g. acceptance and commitment therapy (Hayes 1999)).
4. Other psychologically-oriented therapies (e.g. mixed models of therapy such as CBT and relaxation training).

Comparator interventions

Comparator interventions will include any of the following.

1. Attention placebo (AP): a control condition that is regarded as inactive by both researchers and by participants in a trial.
2. Psychological placebo (PP): a control condition that is regarded as inactive in a trial by researchers but is regarded as active by the participants.
3. Other non-psychological therapies (e.g. pharmacotherapy for depression or anxiety).
4. Treatment as usual (TAU): participants could receive any appropriate medical care during the course of the study on a naturalistic basis, including standard psychological or pharmacotherapeutic care, usual care or no treatment.
5. Waiting list (WL): as in TAU, patients in the WL condition could receive any appropriate medical care during the course of the study on a naturalistic basis.

Types of outcome measures

Outcome measures will be focused on the individual child rather than the wider family. We will evaluate the difference between the treatment group and the control group separately for anxiety and depression using the following outcomes.

Primary outcomes

1. Treatment efficacy: changes in severity of anxiety and depression symptoms separately measured using validated scales for each of these conditions (e.g. Children's Depression Inventory (CDI) for childhood depression (Kovacs 1989); State-Trait Anxiety Inventory (STAI) for anxiety (Spielberger 1983)). Clinician-rated scales will be analysed separately from those rated by children, young people, parents and others (e.g. teachers). Statistically-significant results will be interpreted with regard to the clinical significance of each scale (possibly using T-scores if these are available for all scales).
2. Treatment acceptability: self-reported measure of treatment satisfaction, or if not measured, rates of completion of the intervention.

Secondary outcomes

1. Changes in caseness (remission/response) separately measured using similar validated scales for each of these conditions.
2. Suicide-related behaviour: number of a) deaths by suicide, b) suicide attempts and c) episodes of deliberate self harm, either reported or measured using validated scales (Osman 2001).
3. Improvement in quality of life measured using validated scales (e.g. Paediatric Quality of Life inventory (PedsQL, Varni 2004)
4. Functioning, as a proxy for psychological well-being, measured using validated scales (e.g. Children's Global Assessment Scale (CGAS), Shaffer 1984)
5. Status of long-term physical condition using validated scales (e.g. Paediatric Asthma Symptom Scale (PASS), Lara 2000)).
6. Adherence to treatment of long-term physical condition.
7. School/college attendance (e.g. reduction in number of days missed).
8. Economic benefits (e.g. reduction of costs of treatment, number of appointments with general practitioners, use of additional treatments, ability to study or work).

Timing of outcome assessment

Clustering and comparison of outcome measures at similar time periods will be undertaken. The primary time point will be short-term change (at the end of treatment). Short-term and long-term (three months or more beyond the end of treatment) outcome measures will be assessed separately. If multiple long-term measures have been provided, we will use the one furthest from the intervention as this will be most relevant to understanding the enduring nature of the therapeutic effect.

Hierarchy of outcome measures

For trials presenting a range of symptom measures (e.g. multiple depression scales) we will use the scale ranked highest according to the following five criteria: appropriateness to children and adolescents; reliability; construct validity; agreement with clinical interview; track record in psychopharmacological research.

For depression the ranking from highest to lowest would be as follows: Schedule for Affective Disorders and Schizophrenia for School-Age Children (Kiddie-SADS (Kaufman1997)), Children's Depression Rating Scale (CDRS (Poznanski 1985)), Bellevue Index of Depression (BID (Petti 1978)), Children's Depression Inventory (CDI (Kovacs 1985)), Hamilton Depression Rating Scale (HAM-D (Hamilton 1967)), Depressive Adjective Check-list (DACL (Lubin 1965)), then others (Hazell 2002).

For anxiety, the ranking would be based on appropriateness to children and adolescents, reliability, construct validity, agreement with clinical interview and track record in psychotherapeutic research. From highest to lowest, this would be as follows: Anxiety Disorder Interview Schedule (ADIS (Silverman 1988)), Multidimensional Anxiety Scale for Children (MASC (March 1997)), Paediatric Anxiety Rating Scale (PARS (PARS 2002)), Social Phobia and Anxiety Inventory for Children (SPAI-C (Beidel 2000)), Social Anxiety Scale for Children-Revised (SASC-R (La Greca 1988)), Fear Survey Schedule for Children-Revised (FSSC (Olendick 1983)), Revised Children's Manifest Anxiety Scale (RCMAS (Reynolds 1978)), State-Trait Anxiety Inventory for Children (STAI-C (Spielberger 1973)), Screen for Child Anxiety Related Emotional Disorders (SCARED (Birmaher 1999)), Hamilton Anxiety Rating Scale (HARS (Maier 1988)), then others (based on Myers 2002).

Search methods for identification of studies

Specialised Register of the Cochrane Common Mental Disorders Group (CCMD-CTR)

The Cochrane Common Mental Disorders Group maintains a specialised register of randomised controlled trials, the CCMD-CTR. This register contains over 40,000 reference records (reports of RCTs) for anxiety disorders, depression, bipolar disorder, eating disorders, self-harm and other mental disorders within the scope of this Group. The CCMD-CTR is a partially studies-based register with more than 50% of reference records tagged to approximately 12,500 individually PICO coded study records. Reports of trials for inclusion in the register are collated from (weekly) generic searches of MEDLINE (1950-), Embase (1974-) and PsycINFO (1967-), quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review-specific searches of additional databases. Reports of trials also sourced from international trial registries, drug companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCMD's core search strategies (used to identify RCTs) can be found on the Group's website with an example of the core MEDLINE search displayed in Appendix 1.

Electronic searches

The Cochrane Group's Information Specialist will search the CCMD-CTR using the following terms.

CCMD-CTR-Studies Register

Condition = *(anxiety or depressi* or mood or mutism or neuroses or neurotic or "obsessive compulsive" or panic or *phobi* or psychoneuroses or "stress disorder*" or "psychological stress" or "school refusal")*

and Comorbidity = *not empty*

and Age Group = *(child or adolescent)*

We will screen these records for eHealth-based interventions in this population.

CCMD-CTR-References Register

The Information Specialist will search the references register using a more sensitive set of terms to find additional untagged/uncoded reports of RCTs (Appendix 2).

We will conduct complementary searches on the following bibliographic databases using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.

- The Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO) (Appendix 3).
- Other Cochrane Library databases (CDSR, DARE, HTA).
- Web of Science Core Collection (Science, Social Science and Conference Proceeding indices (SCI, SSCI, CPCI-S, CPCI-SSH)).

We will search international trial registries via the World Health Organization's trials portal (ICTRP) and ClinicalTrials.gov to identify unpublished or ongoing studies.

We will not restrict our search by date, language or publication status.

Searching other resources

Handsearching

We will handsearch relevant conference proceedings (those titles not already indexed in Embase or PsycINFO, or already handsearched within Cochrane) as follows:

- Annual Meeting of the American Academy of Child and Adolescent Psychiatry (AACAP) (2000 onwards); and
- International Conference of the European Federation for Medical Informatics (MIE) (c/o Studies in Health Technology and Informatics journal).

Reference lists

We will check the reference lists of all included studies and relevant systematic reviews to identify additional studies missed from the original electronic searches (for example unpublished or in-press citations). We will also conduct a cited reference search on the Web of Science for reports of all included studies.

Grey literature

We will search sources of grey literature via the following websites: Open Grey www.opengrey.eu/ and the National Guidlines Clearing House www.guideline.gov/

Correspondence

We will contact trialists and subject experts for information on unpublished or ongoing studies or to request additional trial data.

Data collection and analysis

Selection of studies

Two authors (HT and SW) in conjunction with the CCMD editorial office will conduct the search. Two authors (HT and JH) will independently screen the titles and abstracts of the studies identified. Studies that obviously do not fulfil inclusion criteria at this stage of the screening process will be discarded. Eligible or potentially-eligible articles will be retrieved for full-text inspection by two authors (HT and JH) independently. We will resolve any discrepancies by discussion or by involving a third author (KS) as necessary. We will list the reasons for exclusion in the table 'Characteristics of excluded studies'. The selection process will be described in enough detail in order to complete a PRISMA flow diagram.

Data extraction and management

Two authors (HT and KS) will independently extract data on trial characteristics, the methodology, participant characteristics, intervention characteristics, outcome measures and outcome data using a data extraction sheet (Appendix 2) that we will pilot on one included study. We will contact authors to obtain additional information when required. After agreement, data for analysis will be transferred in RevMan 5.3 into the format required to include the maximal numbers of studies (events and total number of patients for each group; mean, standard deviations (SDs) and number of patients included in each group; or generic inverse variance if necessary). Any disagreements will be resolved by discussion or with the help of the third author (SH).

Main planned comparisons

1. eHealth interventions for anxiety or depression versus attention placebo (AP).
2. eHealth interventions for anxiety or depression versus psychological placebo (PP).
3. eHealth interventions for anxiety or depression versus other non-psychological therapies (e.g. pharmacotherapy for depression or anxiety).
4. eHealth interventions for anxiety or depression versus treatment as usual (TAU).
5. eHealth interventions for anxiety or depression versus waiting list (WL).

For definitions of interventions and comparators, see Types of interventions. We will combine all types of eHealth interventions in the main analyses, and conduct subgroup analyses to investigate any differences between them (where data allow).

Assessment of risk of bias in included studies

Risk of bias will be assessed for each included study using Cochrane's 'Risk of bias' tool (Higgins 2011). The following domains will be considered.

1. Sequence generation: was the allocation sequence adequately generated.
2. Allocation concealment: was allocation adequately concealed?
3. Blinding of participants and care providers for each main outcome or class of outcomes: was knowledge of the allocated treatment adequately prevented during the study?
4. Blinding of outcome assessors for each main outcome or class of outcomes: was knowledge of the allocated treatment adequately prevented during the study?
5. Incomplete outcome data for each main outcome or class of outcomes: were incomplete outcome data adequately addressed?
6. Selective outcome reporting: are reports of the study free of any suggestion of selective outcome reporting?
7. Other sources of bias: was the study apparently free of other problems that could put it at high risk of bias? Additional items to be included here are therapist qualifications, treatment fidelity and researcher allegiance/conflict of interest.

A description of what was reported to have happened in each study will be reported independently by two authors (HT and KS) and a

judgement on the risk of bias will be made for each domain within and across studies, based on the following three categories.

- Low risk of bias.
- Unclear risk of bias.
- High risk of bias.

Any disagreement will be resolved by discussion or with the help of the third author (SH). For cluster-randomised trials, the risk of bias will be assessed by considering recruitment bias, baseline imbalance, loss of cluster, incorrect analysis and comparability with individual randomised trials. The level of risk of bias will be noted in both the body of the review and the 'Summary of findings' table.

Measures of treatment effect

Odds ratio (OR) will be used for comparing dichotomous data and standardised mean differences (SMD) for the analysis of continuous data. SMD effect sizes of 0.2 will be considered small, 0.5 will be considered medium and ≥ 0.8 will be considered large (Pace 2011). When an effect is discovered, a number needed to treat for an additional beneficial outcome (NNTB) for the primary outcome will be calculated from the OR (www.nntonline.net/visualrx/) as this value is less likely to be affected by the side (benefit or harm) to which the data are entered (Deeks 2000; Cook 2002).

We will undertake meta-analyses only where this is meaningful i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. We will narratively describe skewed data reported as medians and interquartile ranges. Where multiple trial arms are reported in a single trial, we will include only the relevant arms.

Unit of analysis issues

Cluster-randomised trials

Should any cluster randomised trials be identified, they will be included as long as proper adjustment for the intra-cluster correlation can be undertaken as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Cross-over trials

Due to the risk of carry-over effects in cross-over trials, only data from the first phase of the study will be used.

Studies with multiple treatment groups

Where studies have additional arms that are not eHealth interventions, we will only include the data relating to the therapy and one control arm in the review. If a study has more than two arms that meet the inclusion criteria, for example two eHealth interventions and a control arm, data from the control arm will be split equally to produce two (or more) pairwise comparisons.

Dealing with missing data

We will contact the authors for apparently missing data. We will use ITT analysis where this is reported and will mention in the 'Risk of bias' table whether or not ITT analysis was done. For continuous data, we will use last observation carried forward (LOCF). We will only use imputed data if this is done on the basis of multiple imputation or modelling using maximum likelihood estimation. If necessary, sensitivity analysis will be conducted to ascertain the effect of multiple missing data management techniques. Where trials do not report the SDs of continuous measure scores and the original authors are unable to provide them, we will calculate the SD from the standard error (SE) or P values (Altman 1996), or from CI, t-values or P values as described in section 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If this is not possible, we will use the baseline SD. If means are based on imputed data and are all that is available, we will use n-dropout.

Assessment of heterogeneity

Before pooling results and carrying out any meta-analysis, we will consider clinical heterogeneity and the role of subgroup analyses to address it. We will quantify statistical heterogeneity using the I^2 statistic with data entered in the way (benefit or harm) that yields the lowest amount. The amount, depending on the value obtained for the I^2 statistic (Higgins 2003), will be qualified as:

- might not be important (0 to 40%);
- may represent moderate heterogeneity (30% to 60%);
- may represent substantial heterogeneity (50% to 90%); and
- may represent considerable heterogeneity (75% to 100%).

Assessment of reporting biases

If more than 10 studies are included, their data will be entered into a funnel plot (trial effect versus trial size) in order to evaluate overt publication bias. A symmetrical funnel plot is likely to indicate low publication bias and an asymmetric funnel plot is likely to indicate likely publication bias. The number of studies required to reduce the P value of a statistically-significant finding to 0.05 (not statistically significant) will also be used to evaluate the robustness of the findings. A high classical fail-safe number will indicate that the conclusions are unlikely to be reversed by new studies, while a low classical fail-safe number will indicate that they may be more likely to be reversed in the future. Finally, we will use Duval and Tweedie's trim and fill analysis (Duval 2000) to estimate what the effect size (OR, risk ratio, etc.) would be if there was no publication bias.

Data synthesis

When available and sufficiently clinically- and statistically-homogenous, we will combine data from included trials in meta-analyses. We will present the characteristics of included and excluded studies in tables. We will present the 'Risk of bias' assessment in a 'Risk of bias' graph. As we are anticipating heterogeneity of data, we plan to analyse the data in RevMan 5.3 using a random-effects model. We will present results for each comparison as forest plots when appropriate. We will provide narrative summaries for comparisons with less than two available studies and those with a moderate or high level of statistical heterogeneity following heterogeneity exploration.

Subgroup analysis and investigation of heterogeneity

For each condition (anxiety or depression), in order to better understand the factors that contribute to effective intervention, we will perform subgroup analyses upon the primary outcome as follows.

1. Type of experimental therapy (e.g. CBT, other therapy). This will be undertaken because different types of therapies are known to have varied underlying theoretical bases and often result in different effect sizes (e.g. Watanabe 2007).
2. Type of control therapy (e.g. active comparators such as attention placebo, psychological placebo and other non-psychological therapies) and non-active comparators (such as treatment as usual and waitlist) as defined by previous researchers (Weisz 2006). Control intervention type has been shown to influence effect sizes (e.g. Furakawa 2014).
3. Modality of delivery (e.g. individual, group). Different modalities of therapy have been shown to result in different effect sizes during the treatment of a range of conditions (Wierzbicki 1987).
4. Dose of treatment (number of completed sessions). Although different therapies will have different total durations, it is of interest to identify therapies that most efficiently result in symptomatic improvement.
5. Therapist assistance. There is some evidence that adherence and outcome may be influenced by therapist assistance (Andersson 2009).
6. Form of measurement (e.g. self-rated, parent-rated, clinician-rated). Different types of rating scale have been shown to contribute differently to the prediction of outcomes (Uher 2012).
7. Type of long-term physical conditions (e.g. asthma, diabetes). This will be undertaken to identify whether these therapies are more or less effective for children (0 to 12 years old) and young people (13 to 18 years old) with different types of physical illness and in order to make recommendations regarding the targeted use of these therapies.
8. Category of depressive symptoms. There is a possibility that sub-threshold and threshold depressive symptoms may respond differently to therapies (Costello 1992).
9. Target of intervention. Interventions targeted at children or adolescents may be differently effective to those targeted at families (Aydin 2014).
10. Participant factors (e.g. sex, age). Younger and older people have been shown to have different effect sizes following similar therapies (Bennett 2013) so results will be analysed according to four clinically-relevant subgroups of age (0 to 8, 9 to 12, 13 to 15, and 16 to 18 years old).

The feasibility of undertaking these analyses will depend upon the number, quality and heterogeneity of included studies. All heterogeneity will be explored, but comparisons with moderate and higher heterogeneity (I^2 statistic > 30%) will be further explored using Egger's regression intercept to assess the possibility of a small study effect (Rucker 2011), visual forest plot inspection (with studies plotted in order according to a specific moderator or subgrouping (categorical moderators) or meta-regressions (continuous moderators).

Sensitivity analysis

In order to test the robustness of decisions made during the review process, a sensitivity analysis will be carried out for the primary outcomes only, based on:

1. allocation concealment;
2. dropout rate; and
3. blinding of outcome assessors.

We will run three separate sensitivity analyses: one where we remove those studies at high or unclear risk of bias in the domain of allocation concealment; one where we remove those studies at high or unclear risk of bias in the domain of outcome assessor blinding; and one where we remove those studies at high or unclear risk of bias in the domain of missing data. We will also run a sensitivity analysis where we remove those studies where more than 20% of participants did not complete the post-intervention outcome assessment. The first two have been shown to have the largest impact on treatment effect (Schulz 1995).

'Summary of findings' table

We will construct a 'Summary of findings' table for each comparison between eHealth and other interventions, with regard to the following outcomes.

1. Change in severity of anxiety symptoms at end of treatment (defined as short term).
2. Change in severity of depressive symptoms (short term).
3. Change in quality of life measures (short term).
4. Change in functioning measures (short term).
5. Change in status of long-term physical condition (short term).
6. Dropouts due to adverse effects (short term).
7. Suicide-related behaviour (short term).

In the 'Summary of findings' tables we will use the principles of the GRADE approach (Guyatt 1998) to assess the extent to which there can be confidence that the obtained effect estimate reflects the true underlying effect. The quality of a body of evidence will be judged on the basis of the included studies' risks of bias, the directness of the evidence, unexplained heterogeneity, imprecision, and the risk of publication bias. We will use the average rate in all the arms of included trials as the 'assumed risk' for each outcome. As we are not aiming to target any particularly high- or low-risk populations, all the tables will be for medium-risk populations.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search for Specialised Register

OVID MEDLINE search strategy, used to inform the Cochrane Common Mental Disorders Group's Specialised Register

A weekly search alert based on condition + RCT filter only

1. *[MeSH Headings]:*

eating disorders/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or female athlete triad syndrome/ or pica/ or hyperphagia/ or bulimia/ or self-injurious behavior/ or self mutilation/ or suicide/ or suicidal ideation/ or suicide, attempted/ or mood disorders/ or affective disorders, psychotic/ or bipolar disorder/ or cyclothymic disorder/ or depressive disorder/ or depression, postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/ or neurotic disorders/ or depression/ or adjustment disorders/ or exp antidepressive agents/ or anxiety disorders/ or agoraphobia/ or neurocirculatory asthenia/ or obsessive-compulsive disorder/ or obsessive hoarding/ or panic disorder/ or phobic disorders/ or stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or anxiety/ or anxiety, castration/ or koro/ or anxiety, separation/ or panic/ or exp anti-anxiety agents/ or somatoform disorders/ or body dysmorphic disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/ or hysteria/ or munchausen syndrome by proxy/ or munchausen syndrome/ or fatigue syndrome, chronic/ or obsessive behavior/ or compulsive behavior/ or behavior, addictive/ or impulse control disorders/ or firesetting behavior/ or gambling/ or trichotillomania/ or stress, psychological/ or burnout, professional/ or sexual dysfunctions, psychological/ or vaginismus/ or Anhedonia/ or Affective Symptoms/ or *Mental Disorders/

2. *[Title/ Author Keywords]:*

(eating disorder* or anorexia nervosa or bulimi* or binge eat* or (self adj (injur* or mutilat*)) or suicide* or suicidal or parasuicid* or mood disorder* or affective disorder* or bipolar i or bipolar ii or (bipolar and (affective or disorder*)) or mania or manic or cyclothymic* or depression or depressive or dysthymi* or neurotic or neurosis or adjustment disorder* or antidepress* or anxiety disorder* or agoraphobia or obsess* or compulsi* or panic or phobi* or ptsd or posttrauma* or post trauma* or combat or somatoform or somati# ation or medical* unexplained or body dysmorphi* or conversion disorder or hypochondria* or neurastheni* or hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedoni* or affective symptoms or mental disorder* or mental health).ti,kf.

3. *[RCT filter]:*

(controlled clinical trial.pt. or randomized controlled trial.pt. or (randomi#ed or randomi#ation).ab,ti. or randomly.ab. or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab. or placebo*.ab,ti. or drug therapy.fs. or trial.ab,ti. or groups.ab. or (control* adj3 (trial* or study or studies)).ab,ti. or (singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or randomized controlled trial/ or pragmatic clinical trial/ or (quasi adj (experimental or random*)).ti,ab. or ((wait list* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab.)

4. (1 and 2 and 3)

Records are screened for reports of RCTs within the scope of the Cochrane Common Mental Disorders Group. Secondary reports of RCTs are tagged to the appropriate study record. Similar weekly search alerts are also conducted on OVID Embase and PsycINFO, using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.

Appendix 2. Review search: CCMD-CTR-References Register

The CCMD-CTR-references register will be searched using a sensitive set of terms for: *age group + condition + comorbidity + eHealth platforms/computer programs*:

[Age Group]

#1. (child* or boy* or girl* or infant* or juvenil* or minors or paediatric* or pediatric* or school* or preschool* or pre-school* or kindergarten or nursery or adolesc* or preadolesc* or pre-adolesc* or pubert* or pubescen* or prepub* or pre-pube* or high-school or teen* or (young next (adult* or people or patient* or men* or women* or mother* or male or female or survivor* or offender* or minorit*)) or youth* or student* or undergrad* or college or campus or classroom):*ti,ab*

[Condition: anxiety/depression]

#2. ((emotion* or psycholog* or mental) next (health or stress* or problem* or disturb* or asp* or st* or ill*)):*ti,ab,kw,ky,emt,mh,mc*

#3. (depress* or mood or anxiety or *phobi* or PTSD or post-trauma* or posttrauma or "post traum*" or panic* or OCD or obsess* or compulsi* or GAD or "stress disorder*" or "stress reaction*" or "acute stress" or "psychological stress" or "school refusal" or mutism or neurosis or neuroses or neurotic or psychoneuro*):*ti,ab,kw,ky,emt,mh,mc*

[Comorbidity: chronic physical illnes s]

#4. ("physical* ill*" or "medical* ill*" or "chronic disease" or (chronic* NEXT (ill* or condition*1 or disease* or disorder* or health)) or (long term NEXT (condition*1 or sick*)) or "medical* morbid*" or (medical NEXT (comorbid* or co morbid*)) or multimorbid* or (multi* NEXT (morbid* or "co morbid*" or comorbid* or physical))):*ti,ab,kw,ky,emt,mh,mc*

#5. (AIDS or allerg* or angina or aneurysm or "ankylosing spondylitis" or arthropath* or arthriti* or arthrosis or arthroses or asthma* or "atrial fibrillation" or "autoimmune disease*" or "back pain" or blindness or "brain atroph*" or (bone NEXT (disease* or disorder*)) or ((bronchi* or bowel) NEXT (disease* or disorder*)) or bypass or cancer* or neoplasm* or neoplastic or malignan*) or (cardiac NEXT (arrest or arrhythmia* or surg*)) or cardiomyopath* or ((cardiovascular or coronary) NEAR2 (disease* or disorder* or event*)) or "cerebral palsy" or (cerebrovascular NEAR2 (disease* or disorder* or event*)) or "chronic obstructive" or COPD or pain or cirrhosis or colitis or "congenital abnormalit*" or (congential NEAR3 (disease* or disorder*)) or coxarthrosis or Crohn* or Cushing* or "cystic fibrosis" or cystitis)

#6. (deaf* or deformit* or disabled or (physical NEXT (deform* or disab* or impair*)) or dermatitis or dermato* or dorsopath* or diabet* or "digestive system*" or duoden* or dystonia or eczem* or (endocrine NEXT (disease* or disorder*)) or enuresis or epilep* or "eye disease*" or ("fatigue syndrome" or "chronic fatigue") or fibromyalgia or fibrosis or "food hypersensitivity" or (gastr* NEXT (disease* or disorder*)) or gastritis or "genetic disorder*" or gingivit* or (glomerul* NEXT (disease* or disorder*)) or headache* or ((h?emic or lymph*) NEXT (disease* or disorder*)) or h?emangioma or h?emophili* or h?emorrhag* or ((hearing or visual or vision) NEAR2 (aid* or impair* or loss)) or hemiplegi* or hepatitis or h?emodialysis or ((renal or kidney) NEXT (disease* or disorder* or failure)) or (heart NEXT (disease* or disorder* or failure or surg*)) or HIV or "human immunodeficiency virus" or hypertensi* or hypotensi*)

#7. ("inflammatory disease*" or incontinen* or "irritable bowel" or isch?emi* or (joint NEXT (disease* or disorder*)) or kyphosis or leuk?emia or ((liver or hepatic) NEXT (disease* or disorder* or failure)) or lordosis or "lung disease*" or "lupus erythemat*" or lymphoma or "macular degeneration" or migraine* or "movement disorder*" or musculoskeletal or necrotizing or nephrotic* or neuromuscular or "multiple sclerosis" or myeloma)

#8. ("nephrotic syndrome" or ((nutritional or metabolic) NEXT (disease* or disorder or syndrome*)) or (organ* NEAR2 (transplant* or recipient*)) or (neurological NEXT (disease* or disorder*)) or occlusion* or obesity or obese or orthop?edic* or osteo* or "otitis media" or otorhinolaryngology* or otosclerosis or pancrea* or papulosquamous or paraplegi* or parkinson* or "peripheral vascular" or "pick disease*" or pneumoconiosis or polio* or polyarthropath* or polyarteritis or polyarthrosis or polyneuropath* or psoriasis or parapsoriasis or (pulm* NEAR2 (disease* or disorder*)))

#9. ((respiratory NEXT (disease* or disorder*)) or retinopathy or rheumat* or sclerosis or scoliosis or "sickle cell an?emia" or ((skin or "connective tissue") NEXT (disease* or disorder*)) or ("sleep disorder*" or "sleep apn?ea" or insomnia* or dyssomnia* or hypersomnia*) or "spina bifida" or "spinal muscular atropy" or spondylo* or stenosis* or stoma* or (stroke or strokes or "cerebral infarct*") or tetraplegi* or ((thyroid NEAR (disease* or disorder* or dysfunction*)) or hyperthyroidism or hypothyroidism) or tuberculosis or (systemic NEAR (disorder* or disease*)) or ulcer* or (urogenital NEXT (disease* or disorder*)) or vasculopath* or (vascular NEAR (disease* or disorder*)) or vestibular or ((virus or viral) NEXT disease))

#10. (#1 and (#2 or #3) and (#4 or #5 or #6 or #7 or #8 or #9))

[eHealth]

#11 (android or app or apps or audio* or blog or CBT or CD-ROM or "cell phone" or cellphone or chat or computer* or cyber* or DVD or eHealth or e-health or "electronic health*" or e-Portal or ePortal or eTherap* or e-therap* or forum* or gaming or iCBT or "information technolog*" or "instant messag*" or internet* or ipad or i-pad or iphone or i-phone or ipod or i-pod or web* or WWW or "smart phone" or smartphone or "social network* site*" or "mobile phone" or e-mail* or email* or mHealth or m-health or mobile

or multi-media or multimedia or online* or on-line or "personal digital assistant" or PDA or SMS or "social medi*" or software or telecomm* or telehealth* or telemed* or telemonitor* or telephone or telepsych* or teletherap* or "text messag*" or texting or podcast or virtual*):ab,ti,kw,ky,emt,mh,mc

#12 ("Brave for Teen*" or "Brave for Child*" or "Camp Cope-A-Lot" or "Cool Teens" or Interapy or Memo or Minded or Mindcheck* or "Mood Gym" or Moodgym or Moodhelper or "Mood Helper" or Sparx or "The Journey" or "Think Feel Do")

#13 (Bebo or "Club Penguin" or Facebook or Franktown or Friendster or Habbo or Jabbersmack or hi5 or iTwixie or MySpace or Orkut or "Sweety High" or Kidzworld or Tumblr or Twitter or Sina Weibo or Yoursphere or YouTube)

#14 (#11 or #12 or #13)

#15 (#10 and #14)

Key to field codes:

ti: title; ab: abstract; kw: CCMD keywords; ky: additional keywords; emt: EMTREE subject headings; mh:MeSH subject headings; mc: MeSH check words

Appendix 3. Review search: CENTRAL search (via CRSO)

The Cochrane Central Register of Controlled Trials (CENTRAL) will be searched via the Cochrane Register of Studies Online (CRSO)), using a sensitive set of terms for age group, condition, comorbidity and intervention:

[Age Group]

#1 (child* or boy* or girl* or infant* or juvenil* or minors or paediatric* or pediatric* or school* or preschool* or pre-school* or kindergarten or nursery or adolesc* or preadolesc* or pre-adolesc* or pubert* or pubescen* or prepube* or pre-pube* or high-school or teen* or (young next (adult* or people or patient* or men* or women or mother* or male or female or survivor* or offender* or minorit*)) or youth* or student* or undergrad* or college or campus or classroom):ti,ab

[Condition: anxiety/depression]

#2 ((emotion* or psycholog* or mental) next (health or stress* or problem* or disturb* or aspect* or state* or ill*))

#3 (depress* or mood or anxiety or *phobi* or PTSD or post trauma* or posttrauma or "post trauma*" or panic* or OCD or obsess* or compulsi* or GAD or "stress disorder*" or "stress reaction*" or "acute stress" or "psychological stress" or "school refusal" or mutism or neurosis or neuroses or neurotic or psychoneuro*)

[Comorbidity: chronic physical illness]

#4 ("physical* ill*" or "medical* ill*" or "chronic disease*" or (chronic* NEXT (ill* or condition*1 or disease* or disorder* or health)) or (long term NEXT (condition*1 or sick*)) or "medical* morbid*" or (medical* NEXT (comorbid* or co morbid*)) or multimorbid* or (multi* NEXT (morbid* or "co morbid*" or comorbid* or physical)))

#5 (allerg* or angina or aneurysm* or "ankylosing spondylitis" or arthropath* or arthriti* or arthrosis or arthroses or asthma* or "atrial fibrillation" or "autoimmune disease*" or "back pain" or blindness or "brain atroph*" or (bone NEXT (disease* or disorder*)) or ((bronchi* or bowel) NEXT (disease* or disorder*)) or bypass or (cancer or neoplasm* or neoplastic or malignan*) or (cardiac NEXT (arrest or arrhythmia* or surg*)) or cardiomyopath* or ((cardiovascular or coronary) NEAR2 (disease* or disorder* or event*)) or "cerebral palsy" or (cerebrovascular NEAR2 (disease* or disorder* or event*)) or "chronic obstructive" or COPD or pain or cirrhosis or colitis or "congenital abnormalit*" or (congential NEAR3 (disease or disorder*)) or coxarthrosis or Crohn* or Cushing* or "cystic fibrosis" or cystitis)

#6 (deaf* or deformit* or disabled or (physical NEXT (deform* or disab* or impair*)) or dermatitis or dermato* or dorsopath* or diabet* or "digestive system" or duoden* or dystonia or eczema or (endocrine NEXT (disease* or disorder*)) or enuresis or epilep* or "eye disease*" or "fatigue syndrome" or "chronic fatigue") or fibromyalgia or fibrosis or "food hypersensitivity" or (gastr* NEXT (disease* or disorder*)) or gastritis or "genetic disorder*" or gout or (glomerul* NEXT (disease* or disorder*)) or headache* or ((h?emic or lymph* NEXT (disease* or disorder*)) or h?ematuria or h?emophili* or h?emorrhag* or ((hearing or visual or vision) NEAR2 (aid* or impair* or loss)) or hemiplegi* or hepatitis or h?emodialysis or ((renal or kidney) NEXT (disease* or disorder* or failure)) or (heart NEXT (disease* or disorder* or failure or surg*)) or HIV or "human immunodeficiency virus" or hypertensi* or hypotensi*)

#7 ("inflammatory disease*" or incontinen* or "irritable bowel" or isch?emi* or (joint NEXT (disease* or disorder*)) or kyphosis or leuk?emia or ((liver or hepatic) NEXT (disease* or disorder* or failure)) or lordosis or "lung disease*" or "lupus erythemat*" or lymphoma or "macular degeneration" or migraine* or "movement disorder*" or musculoskeletal or necrotizing or nephrotic* or neuromuscular or "multiple sclerosis" or myeloma)

#8 ("nephrotic syndrome" or ((nutritional or metabolic) NEXT (disease* or disorder or syndrome*)) or (organ* NEAR2 (transplant* or recipient*)) or (neurological NEXT (disease* or disorder*)) or occlusion* or obesity or obese or orthop?edic* or osteo* or "otitis media" or otorhinolaryngology* or otosclerosis or pancrea* or papulosquamous or paraplegi* or parkinson* or "peripheral vascular"

or "pick disease*" or pneumoconiosis or polio* or polyarthropath* or polyarteritis or polyarthrosis or polyneuropath* or psoriasis or parapsoriasis or (pulmonary NEAR2 (disease* or disorder*)))
#9 ((respiratory NEXT (disease* or disorder*)) or retinopathy or rheumat* or sclerosis or scoliosis or "sickle cell an?emia" or ((skin or "connective tissue") NEXT (disease* or disorder*)) or ("sleep disorder*" or "sleep apn?ea" or insomnia* or dyssomnia* or hypersomnia*) or "spina bifida" or "spinal muscular atropy" or spondylo* or stenosis* or stoma* or (stroke or strokes or "cerebral infarct*") or tetraplegi* or ((thyroid NEAR (disease* or disorder* or dysfunction*)) or hyperthyroidism or hypothyroidism) or tuberculosis or (systemic NEAR (disorder* or disease*)) or ulcer* or (urogenital NEXT (disease* or disorder*)) or vasculopath* or (vascul* NEAR (disease* or disorder*)) or vestibular or ((virus or viral) NEXT disease))
#10 ((#1 and (#2 or #3) and (#4 or #5 or #6 or #7 or #8 or #9))
[Intervention: psychological therapies]
#11 MESH DESCRIPTOR Psychotherapy EXPLODE ALL TREES
#12 ((psychologic* or behavio?r or cognitive) adj3 (intervent* or therap* or treat* or m*g*)):ti,ab
#13 (abreaction or "acting out" or (acceptance NEAR2 commitment) or "activity scheduling" or adlerian or "analytical therap*" or "anger control" or "anger management" or "art therap*" or "assertive* training" or "attention bias modification" or "autogenic training" or autosuggestion or "aversion therap*" or "balint group" or "behavio* activation" or "behavio* contracting" or "behavio* modification" or "behavio* therap*" or bibliotherap* or "body therap*" or "brief therap*" or catharsis or "client cent* therapy" or "cognitive behavio*"or "cognitive therap*" or CBT or cCBT or iCBT or "cognitive rehabilitation" or "cognitive restructur*" or "colour therap*" or "color therap*" or "compassion focus*" or "compassionate therap*" or "conjoint therap*" or "contingency management" or "conversion therap*" or "conversational therap*" or countertransference or "coping skill*" or counsel* or "covert sensitization" or "crisis intervention" or "crisis management")
#14 ((dialectic* NEAR2 therap*) or "diffusion therap*" or "distraction therap*" or (dream* NEAR3 analys*) or "eclectic therap*" or "emotion* focus* therap*" or "emotional freedom technique" or "encounter group therap*" or existential or experiential or "exposure therap*" or "expressive therap*" or "eye movement desensitization" or "family therap*" or "focus oriented" or "free association" or freudian or "functional analysis" or gestalt or griefwork or "group therap*" or "guided image*" or "holistic therap*" or humanistic or hypnosis or hypnotherapy or hypnoti#zability or "implosive therap*" or "insight therap*" or "integrative therap*" or "interpersonal therap*" or Jungian or kleinian)
#15 (logotherap* or "logo therap*" or meditation or "mental healing" or metacognitive or meta-cognitive or milieu or "mind train*" or mindfulness or morita or "multimodal therap*" or music or "narrative therap*" or "nondirective therap*" or non-directive therap* or "nondirective therap*" or "non-specific therap*" or "nonspecific therap*" or "object relations" or "personal construct therap*" or "person cent* therap*" or "persuasion therap*" or "play therap*" or "animal therap*" or "play therap*" or ((pleasant or pleasing) NEAR2 event*) or "present cent* therap*" or "primal therap*" or "problem focus* therap*" or "problem sol*" or "process experiential" or psychoanaly* or psychodrama or psychodynamic or psychoeducat* or psychotherap*)
#16 ("rational emotive" or "reality therap*" or "reciprocal inhibition" or "relationship therap*" or "relaxation stress management" or "relaxation technique*" or "relaxation therap*" or "relaxation training" or "reminiscence therap*" or rogerian or "role play*" or schema or "self analys*" or "self esteem building" or "sensitivity training" or "sleep phase chronotherap*" or "socioenvironment* therap*" or "social skill*" or sociotherap* or "solution focused therap*" or "stress management" or "support group*" or (support NEAR3 psycho*) or "supportive therap*" or "systematic desensiti*" or "systemic *therap*" or "therapeutic communit*" or "therapeutic technique" or "third wave" or "time limited therap*" or "transference therap*" or "transactional analysis" or transtheoretical or "validation therap*")
[Intervention: eHealth]
#17 (Bebo or "Club Penguin" or Facebook or Franktown or Friendster or Habbo or Jabbersmack or hi5 or iTwixie or MySpace or Orkut or "Sweety High" or Yidzworld or Tumblr or Twitter or Sina Weibo or Yoursphere or YouTube)
#18 ("Brave for Teens" or "Brave for Child*" or "Camp Cope-A-Lot" or "Cool Teens" or Interapy or Memo or Minded or Mindcheck* or "Mood Gym" or Moodgym or Moodhelper or "Mood Helper" or Sparx or "The Journey" or "Think Feel Do")
#19 (android or app or apps or blog or "cell phone" or cellphone or "chat room" or computer* or cyber* or DVD or eHealth or e-health or "electronic health*" or e-Portal or ePortal or eTherap* or e-therap* or forum* or gaming or cCBT or iCBT or "information technolog*" or "instant messag*" or internet* or ipad or i-pad or iphone or i-phone or ipod or i-pod or web* or WWW or "smart phone" or smartphone or "social network* site*" or "mobile phone" or e-mail* or email* or mHealth or m-health or mobile or multi-media or multimedia or online* or on-line or "personal digital assistant" or PDA or SMS or "social medi*" or software or telecomm* or telehealth* or telemed* or telemonitor* or telepsych*or teletherap* or "text messag*" or texting or podcast or virtual*)
#20 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21 (#10 AND #20)

Appendix 4. Data extraction table

General summary of studies page	
Study ID	
INTERVENTION	
PASSIVE (WL; NT)	
ACTIVE (TAU; AP; Other psych)	
Characteristics of sample page	
RCT or cRCT	
ICC - for cRCTs only	
Inclusion on the basis of diagnosis or elevated symptoms or both	
Tool used if elevated symptoms	
If inclusion on basis of elevated symptoms, what is a cut point specified	
How was diagnosis made (clinical interview, Kiddie SADS, etc.)	
Was comorbid depression included?	
Or was comorbid anxiety excluded?	
Was comorbid substance use excluded?	
Was comorbid psychosis excluded?	
Was comorbid conduct disorder or ODD excluded?	
Was suicide risk excluded?	
Any other comorbid psychiatric disorders excluded	
Baseline severity of depression: state score and the outcome measure	
Baseline severity of anxiety: state score and the outcome measure	
Baseline severity of depression	None, mild, moderate, severe

(*Continued*)

Baseline severity of anxiety	None, mild, moderate, severe
Physical illness 1	
Physical illness 2	
Physical illness 3	
Country	
Source - hospital, outpatient setting, etc.	
Mean age	
Age range bottom	
Age range top	
% male	
Type of psychological approach	
1ry intervention	Behavioural; CBT; 3rd wave; IPT; Other
2nd intervention (if available)	Behavioural; CBT; 3rd wave; IPT; Other
Passive comparison 1	
Passive comparison 2	
Active comparison 1	
Active comparison 2	
Active comparison 3	
Active comparison 4	
Interventions and comparisons page	
Type of psychological approach	Behavioural; CBT; 3rd wave; IPT; Other
Device used for access	Computer, smartphone, other

(*Continued*)

Type of intervention	Website, app, game, other
Name of program	
Dose: length and number of modules or sessions (e.g. 12 x 90min modules or sessions)	
Dose: 8 or more modules or sessions vs. less than 8 modules or sessions	
Dose: total number of hours	
Extra therapist involvement (Yes/No/How much)	
Manualised vs. not manualised	
Reference made to theory/previous seminal work (Beck, Ellis) - Explanatory model stated	
Includes good dose of cognitive restructuring	
Includes good dose of behavioural activation	
Includes general problem solving	
Includes social skills (social problem solving, social skill's training, assertiveness training)	
Includes relaxation	
Includes 3rd wave CBT techniques e.g. mindfulness, distancing	
Includes distress tolerance	
Includes stress management/anxiety management	
Includes biofeedback etc.	
Length of intervention: over what period of time was intervention delivered	
Parent component	
Group vs. individual	
Group: size of group	

(*Continued*)

Delivered by: mental health expert vs. non mental health expert vs. student	
Type of comparison: NT, WL, TAU/UC, other psychological intervention; other intervention; attention placebo	
Describe TAU/UC	
Describe AP	
Is AP credible: does the AP control for: 1. being in a trial; 2. time off class; 3. regular time with an interested adult; 4. being in a group.	
Describe other psychological	
Describe 'other' intervention e.g. Rx	
Risk of bias page	
Randomisation sequence	Low vs. high vs. unclear, Quote
Allocation concealment	Low vs. high vs. unclear, Quote
Performance bias	Low vs. high vs. unclear, Quote
Blinding of participants and care providers (important for self-report depression severity data) - subjective outcomes	Low vs. high vs. unclear, Quote
Blinding of outcome assessors (for assessor rated - not self-rated - depression severity and diagnosis) - objective outcomes	Low vs. high vs. unclear, Quote
Incomplete outcome data	% missing data (% who did not do post-intervention assessment) Method of imputation (OC, LOCF, multiple imputation) ITT analysis Low vs. high vs. unclear (If % missing < 10% rate low; if > 10% but they use multiple imputation and present these data rate low; if > 10% and they use OC or LOCF rate unclear)
Selective outcome reporting	Low vs. high vs. unclear, Quote
Intervention integrity/fidelity	Was it assessed (e.g. taping of sessions and ratings of these tapings) Was it reported Was it adequate

(*Continued*)

Conducted by the researcher who developed the intervention (bias)	
Outcomes page	
Is there follow-up?	Yes/No and describe (e.g. 3 and 6 mths
Diagnosis established how - interview/scale/other	
Data reported/data reported in usable format	
Self report measure	BDI, CDI, CES-D, RADS, MFQ, Other
Data reported/data reported in usable format	
Clinician report measure of depression	
Data reported/data reported in usable format	
Anxiety self-rated measure	BAI, Other
Data reported/data reported in usable format	
Clinician report measure of anxiety	
Data reported/data reported in usable format	
Functioning measure	CGAS, SOFAS, Other
Other outcomes	
Number randomised at baseline	Intervention Control
Number who completed post intervention assessment for primary outcome	Intervention Control
% missing data for risk of bias	
Number who started intervention and control arms	Intervention Control
Number who dropped out of treatment and control groups	Intervention Control

(*Continued*)

Post and follow-up self-report depression/anxiety diagnosis page	
Post-intervention Treatment group post-intervention Control post-intervention	Mean, SD, N Mean, SD, N
Medium term Treatment Control	Time point for medium i.e. 6 months or 12 months after post-assessment Mean, SD, N Mean, SD, N
Long term Treatment Control	Time point for long term i.e. over 12 months Mean, SD, N Mean, SD, N
Post-intervention clinician data for depression/anxiety diagnosis page	
Number randomised at baseline	Intervention Control
Intervention	Events Total
Control	Events Total
Number included in short-term FU analysis (0 to 3 months)	Intervention Control
Short-term FU number with depressive diagnosis	Intervention Control
Timing	Intervention Control
Number included in medium-term FU analysis (4 to 12 months)	Intervention Control
Medium-term FU number with depressive diagnosis	Intervention Control
Number included in long-term FU analysis (> 12 months)	Intervention Control
Long-term FU number with depressive diagnosis	Intervention Control

(*Continued*)

Post and follow-up depression/anxiety	
Number randomised at baseline	Intervention Control
Number included in post-intervention analysis	Intervention Control
Post-intervention mean	Intervention Control
Post-intervention SD	Intervention Control
Number included in short-term FU analysis (0 to 3 months)	Intervention Control
Short-term FU mean	Intervention Control
Short-term FU SD	Intervention Control
Number included in medium-term FU analysis (4 to 12 months)	Intervention Control
Medium-term FU mean	Intervention Control
Medium-term FU SD	Intervention Control
Number included in long-term FU analysis (> 12 months)	Intervention Control
Long-term FU mean	Intervention Control
Long-term FU SD	Intervention Control
Anxiety/depression and functioning page	
Number randomised at baseline	Intervention Control

(*Continued*)

Number included in post-intervention analysis	Intervention Control
Post-intervention mean	Intervention Control
Post-intervention SD	Intervention Control
Number included in short-term FU analysis (0 to 3 months)	Intervention Control
Short-term FU mean	Intervention Control
Short-term FU SD	Intervention Control
Number included in medium-term FU analysis (4 to 12 months)	Intervention Control
Medium-term FU mean	Intervention Control
Medium-term FU SD	Intervention Control
Number included in long-term FU analysis (> 12 months)	Intervention Control
Long-term FU mean	Intervention Control
Long-term FU SD	Intervention Control

CONTRIBUTIONS OF AUTHORS

Task	Who has agreed to undertake the task?
Draft the protocol	Hiran Thabrew
Develop a search strategy (in conjunction with CCMDs Information Specialist)	Hiran Thabrew, Karolina Stasiak, Stephen Wong

(*Continued*)

Select which trials to include (2 people + 1 arbiter in the event of dispute)	Hiran Thabrew, Karolina Stasiak + Stephen Wong
Extract data from trials (2 people + 1 arbiter in the event of dispute)	Hiran Thabrew, Karolina Stasiak + Stephen Wong
Undertake 'Risk of bias' assessments (2 people + 1 arbiter in the event of dispute)	Hiran Thabrew, Sarah Hetrick, Karolina Stasiak
Enter data into RevMan (Cochrane software)	Hiran Thabrew, Karolina Stasiak
Carry out the analysis	Hiran Thabrew, Sarah Hetrick
Interpret the analysis	Hiran Thabrew, Sarah Hetrick, Sally Merry
Draft the final review	Hiran Thabrew with contribution from Karolina Stasiak, Sarah Hetrick, Sally Merry
Produce the 'Summary of findings' tables	Hiran Thabrew
Check final review meets all mandatory MECIR standards before submission	Hiran Thabrew
Keep the review up to date	Hiran Thabrew, Karolina Stasiak, Sarah Hetrick, Sally Merry

DECLARATIONS OF INTEREST

Sally Merry and Karolina Stasiak have been involved in designing and trailing SPARX, an online and CD-ROM based interactive health game for adolescents with depression.

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