Digital Mental Health Interventions: Are they worth it?

Costs and **O**utcomes of **D**igital **I**nterventions (CODI) to Promote and Improve Mental Health: Evidence Review and Synthesis, Decision Modelling and Knowledge Transfer

Protocol
(version 1, 01 August 2018)

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SUMMARY OF RESEARCH

Digital mental health interventions (DMHIs) use software programmes accessed via computers, smartphones, audio-visual equipment and other devices, to deliver interventions that aim to prevent and improve mental health problems, such as depression, anxiety, addiction and eating disorders. NHS investment on digital technologies is growing. This is particularly important for mental health care where access to services is limited and face-to-face contact with psychiatrists and psychologists is at a premium. Potential investment in digital technologies is large and irreversible, so we need to understand under what circumstances these technologies are conducive to efficient and effective delivery of mental health care and the degree of certainty about the conclusions regarding their cost-effectiveness.

Hundreds of clinical studies provide evidence of improved outcomes with DMHIs, especially for common mental health problems, such as depression and anxiety disorders, but also for addictive behaviours and eating disorders. Economic evaluations (EEs) can provide evidence as to whether DMHIs are good value for money, based on their costs and outcomes relative to the costs and outcomes of alternative care options. No review has so far given a comprehensive picture of whether DMHIs are "good value for money", across all populations, technologies and interventions, especially in the long-term.

Our main aim is to identify and summarise all published and unpublished economic studies comparing the costs and outcomes of DMHIs to the costs and outcomes of alternatives (e.g. interventions without digital technologies or no intervention). We will also develop a taxonomy for categorising DMHIs. Finally, we will explore how economic and clinical evidence is understood and used by key stakeholders in making decisions about the future development, evaluation and adoption of such interventions.

In a collaboration between the Centre for Health Economics, the Centre for Reviews and Dissemination and the Department of Health Sciences at the University of York, we will deliver an 18 month project with 4 work-streams (WS).

- WS1 is a systematic review, critical appraisal and narrative synthesis of all available economic evidence on DMHIs.
- WS2 is a systematic review, narrative synthesis and, when appropriate, quantitative analysis of RCTs and observational studies for a sub-set of DMHIs where the most and best quality clinical evidence exists but without matching economic evidence.
- WS3 considers an economic modelling exercise that quantifies the short- and long-term cost-effectiveness of selected DMHIs followed by a value of information (VoI) analysis, using data from WS1 and WS2.
- WS4 is a series of knowledge exchange workshops with four groups of stakeholders where we will communicate our findings and explore how each stakeholder group understands, interprets and may potentially use these findings.

Apart from peer-reviewed publications and a HTA report, our project will produce a step-by-step guide and an assessment checklist specific to EEs of DMHIs. We will also produce evidence briefings and a proposal for improving science communication with different stakeholder audiences to help them make sense of economic evidence and use this evidence to make decisions about DMHIS within a resource constrained system like the NHS.

1. BACKGROUND AND RATIONALE

DIGITAL MENTAL HEALTH INTERVENTIONS (DMHIs)

DMHIs use software programmes accessed via computers, tablets, smartphones, audio-visual and virtual reality equipment, gaming consoles, robots and other devices, to deliver interventions that aim to prevent or improve mental health problems, including depression, anxiety disorders, addictive behaviours and eating disorders. An example of DMHIs is computerised cognitive behaviour therapy (cCBT), which uses software to deliver standardised therapy programmes with no or little support from a therapist (Gega & Gilbody, 2015). cCBT collects, stores and retrieves clinical information, deliver standardised therapy instructions via text, voice-files or video-clips, and guide patients in the application of therapeutic techniques to achieve personalised goals.

Although DMHIs can be delivered independently of a clinician, software-based programmes and clinicians are not mutually exclusive. DMHIs can be placed in a continuum of varying levels of standardisation, self-help, and clinician involvement. At one end of the continuum, standardised, software-based self-help is independent of a clinician. At the other end of the continuum, clinician can use email, skype or chat-room media to communicate with patients. In the middle of the continuum, blended DMHIs are hybrids of software-based self-help and clinician contact.

The NHS investment in digital technologies is growing rapidly. Under the National Information Board's strategy for Personalised Health and Care 2020, a digital health service will use technology to improve patient choices, access to services, clinical outcomes and better self-care through online services, rather than having to visit a health professional. This is particularly important for mental health care where access to services is limited and face-to-face contact with psychiatrists and psychologists is at a premium. There is an assumption that DMHIs offer “good value for money” because they have the potential to save clinician time and make clinical work more efficient by encouraging patient self-management, allowing remote delivery of interventions, enabling less specialist workforce to deliver complex interventions, enhancing outcomes for the same level of therapeutic input and reducing waiting lists.

DECISION-MAKING UTILISING COST-EFFECTIVENESS EVIDENCE

The decision to adopt DMHIs into a health care system is, at least in part, informed by an assessment of value for money. Cost-effectiveness analyses (CEA) can provide evidence to support or refute the assumption that DMHIs are a good value for money, by comparing the costs and outcomes of DMHIs relative to the costs and outcomes of relevant alternatives. Outcomes in CEAs are often expressed in terms of Quality Adjusted Life Years (QALYs), which are generated by multiplying years of life by the Health Related Quality of Life (HRQoL) score associated with that health state. Costs are calculated by multiplying resources incurred (resource utilisation) over an appropriate time horizon (e.g. visits to the GP over 6 months) by the price attached to each unit of that resource (unit cost). The type of resources included in the final cost calculation depends on the perspective of the economic evaluation; i.e. who pays for, or saves from, the resources used that we are interested in, such as the society in general or the health service in particular.

Once the costs and outcomes of competing alternatives have been estimated, standard decision rules can be used to conclude if a DMHI should be adopted (Karlsson & Johannesson, 1996). If CEAs

demonstrate that DMHIs are likely to be both more effective and less costly than the alternatives, then DMHIs are the preferred option in terms of "value for money". With cCBT as a case in point, two economic evaluations found cCBT to be more effective and less costly compared to usual care for the reduction of gastrointestinal symptoms in patients with irritable bowel syndrome (Andersson et al, 2011), and compared to group CBT for the reduction of panic severity (Bergström et al, 2010).

Decision-making is more complex if DMHIs yield better outcomes for a greater cost compared to their alternatives. This was the case in several economic evaluations of cCBT, in which it was found to be more effective but also more costly than usual care for depression (McCrone et al, 2004) and panic (Olmstead et al, 2010), than relaxation for obsessive compulsive disorder (OCD) (McCrone et al, 2007) and than waiting list for depression (Warmedam et al, 2010). Where costs are higher and QALYs higher, or costs lower and QALYs lower, the incremental gain for a DMHI (costs saved or QALYs gained) must be assessed according to the marginal productivity of the health care system; i.e. how much health is gained with an increase in expenditure at the margin, or how much health is lost with a decrease in expenditure at the margin. An acceptable cost per QALY has been quoted at $50,000 (Grosse, 2008) and £20,000-£30,000 (NICE, 2013).

Making a choice in favour of DMHIs - even when they are likely to be cost-effective – may imply the sacrifice of alternative options. This comes with several problems. First, we may not be able to forego / replace the alterative intervention with DMHIs for ethical, clinical or feasibility reasons; e.g. we cannot prohibit patients from seeing their family doctor in favour of following self-management at home. Second, spending for DMHIs is often frontloaded (e.g. cost of software and hardware), whereas savings or improved outcomes are accrued in the long-run, and payers may not have the money to invest upfront. Third, costs may be incurred in one sector and benefits or savings in another, though their budgets may not be linked (e.g. costs for DMHIs are paid by the health service but savings are accrued in the employment sector because of less absenteeism). In conclusion, health care providers and users may not adopt DMHIs even when they are proven cost-effective, because this will require either dis-investing from existing care options that cannot be foregone, or generating "new monies" to add DMHI to existing care options.

DECISION-MAKING UNDER CONDITIONS OF UNCERTAINTY

An additional consideration for decision-making utilising cost-effectiveness evidence is uncertainty. This uncertainty pertains to the evidence-base used to generate estimates of cost-effectiveness as well as assumptions that are required in compiling this evidence. In order to inform decision making, we need to characterise this uncertainty appropriately, for example using probabilistic sensitivity analysis and/or scenario analyses, and we need to explore the implications of this uncertainty in terms of adoption decisions and recommendations for further research (Claxton, 1999). The evidence-base to support assessments of cost-effectiveness for DMHIs is likely to be less developed, than say pharmaceuticals, because of different regulatory requirements associated with adoption of digital health interventions compared to pharmaceuticals. This implies that an assessment of cost-effectiveness for DMHIs should reflect this uncertainty and communicate it appropriately to decision makers.

EXISTING REVIEWS AND GAPS IN EVIDENCE

Reviews of cost-effectiveness analyses summarise all relevant available economic evidence to inform decisions about the use of scarce resources to support, or not, DMHIs in routine care. The first systematic review of economic evidence for DMHIs was published by the National Institute of Health and Care Excellence (NICE) over 10 years ago (Kaltenthaler et al, 2006) and included only one CEA available at the time, which was on computerised cognitive behaviour therapy (CBT)(McCrone et al, 2004). More recent syntheses of economic evidence relating to DMHIs focus on a specific technology, e.g. the internet (Donker et al, 2015; Arnberg et al, 2014; Tate et al, 2009), or a specific intervention, e.g. CBT (Hedman et al, 2014), or a specific problem, e.g. smoking (Chen et al, 2012), or on physical health (Badawy & Kuhns, 2016; De la Torre-Díez et al, 2015).

We have conducted a scoping literature search to get a sense of the number of CEAs with a mental health primary outcome in peer-reviewed journals. We have found just over 40 CEAs in contrast to the hundreds of clinical trials of DMHIs (without a CEA) and the thousands of DMHI products (without a clinical trial or a CEA). The number of CEAs of DMHIs is likely to be much higher if we capture emerging studies not yet published and grey literature (e.g. doctorate theses), or if we include studies in which mental health is a secondary outcome. Still, the number of CEAs is likely to remain a fraction of that of clinical trials of DMHIs. Many clinicians who conduct clinical trials on DMHIs have neither the knowledge to conduct CEAs nor access to expert health economists. There may also be a lack of understanding on the importance of assessing cost-effectiveness. A step-by-step guide will be helpful to promote the need for good quality CEAs of DMHIs.

No review has so far given a comprehensive picture of the totality of economic evidence for the use digital technologies to support mental health care, irrespective of the targeted population or type of technologies and interventions used. Such a review would be useful, not least because the potential investment in digital technologies is large and irreversible. The economic evidence-base for DMHIs is uncertain, so we need to understand under what circumstances these technologies are conducive to efficient delivery of care and the degree of certainty in the conclusions regarding cost-effectiveness. There may also be particular core assumptions that are key to determining the cost-effectiveness of DMHIs, such as engagement with DMHIs by patients (which can considerably change outcomes) and varied provision of “human support” as an adjunct to DMHIs (which can considerably change the cost e.g. if support is given by specialist clinicians or lay people).

Previous work (McNamee et al, 2016) has concluded that CEAs for digital health interventions (not specific to, but including, mental health) may require more flexible approaches to reflect the complexity of the intervention and its outcomes. Data to inform such CEAs may not capture all of the information required to assess cost-effectiveness. In most CEAs for DMHIs, time horizons are short, and the full opportunity costs of DHIs, such as development costs, are not usually captured. Wider social costs, including productivity losses, presenteeism and other intangible costs, which carry weight in mental health, are also inconsistently measured. In addition, CEAs rarely estimate the investment sum needed for implementing DMHIs or the budgetary impact of their implementation against existing alternatives.

To our knowledge there is no consideration of the appropriateness of existing methods of CEA to assess the value of DMHIs. To do so requires a comprehensive overview and critique of the cost-effectiveness evidence relating to the use of digital technologies to promote or improve mental health outcomes. Such a review will help to highlight the key conditions that make DMHIs cost-effective based on current evidence, as well as to identify key issues for consideration in establishing their cost-effectiveness. The results of a review and critique can be used to generate a guidance and checklist for future CEAs of DMHIs.

STAKEHOLDER UNDERSTANDING AND USE OF COST-EFFECTIVENESS EVIDENCE

We do not know how stakeholders, such as commissioners, practitioners, managers, patients, technologists and researchers, make sense of existing economic evidence about DMHIs and how they will potentially use this evidence to inform their decisions to adopt, optimise or reject certain DMHIs. Many health economics concepts, e.g. QALYs, uncertainty, ICERs, cannot be easily understood or can be easily misunderstood; even the most basic message of an intervention being “cost-effective” is often taken to mean “cheap” or “cost-saving”. Technological advances drive the development and optimisation of DMHIs but not necessarily because it makes clinical or economic sense; e.g. artificial intelligence promotes automated diagnosis which can be more costly and as effective as a basic software-based system that only gathers and relays information for a clinician to make a diagnosis. The above examples highlight that cost-effectiveness evidence for DMHIs can make a meaningful contribution to decision-making when this evidence is effectively communicated to and understood by those who will fund, use or develop DMHIs.

2. AIMS AND OBJECTIVES

Our main aim is to make best use of existing evidence so that we can a) inform practice and future research about which DMHIs are likely to represent a good use of healthcare resources, b) evaluate how uncertain the evidence regarding their cost-effectiveness is, and c) determine what drives variation in their value for money. Our secondary aim is to explore how current economic and clinical evidence is understood and used by key stakeholders in making decisions about the future development, evaluation and adoption of DMHIs.

Our objectives are:

1. To identify and summarise all published and unpublished CEAs comparing the costs and outcomes of DMHIs for the prevention and treatment of any mental health condition to the costs and outcomes of relevant alternatives (e.g. interventions that do not involve digital technologies or no intervention).

2. To identify key drivers of variation in the effects and costs of DIMHs (e.g. for different population sub-groups, delivery methods, economic perspectives or outcome measures).

3. To develop classification criteria to inform a taxonomy for categorisation of digital mental health interventions.

4. To critically evaluate the quality and appropriateness of the methods used by existing CEAs to establish the cost-effectiveness of DMHIs.

5. To determine what cost-effectiveness judgements can be made for DMHIs given current evidence from EEs.

6. To conduct an exploratory analysis to quantify the short- and long-term cost-effectiveness of DMHIs using a *de-novo* decision analytic model informed by a systematic review and quantitative data synthesis of clinical trials on common mental health problems.

7. To conduct a value of information (VoI) analysis based on the decision model findings and make recommendations as to what further research is necessary to inform future decisions.

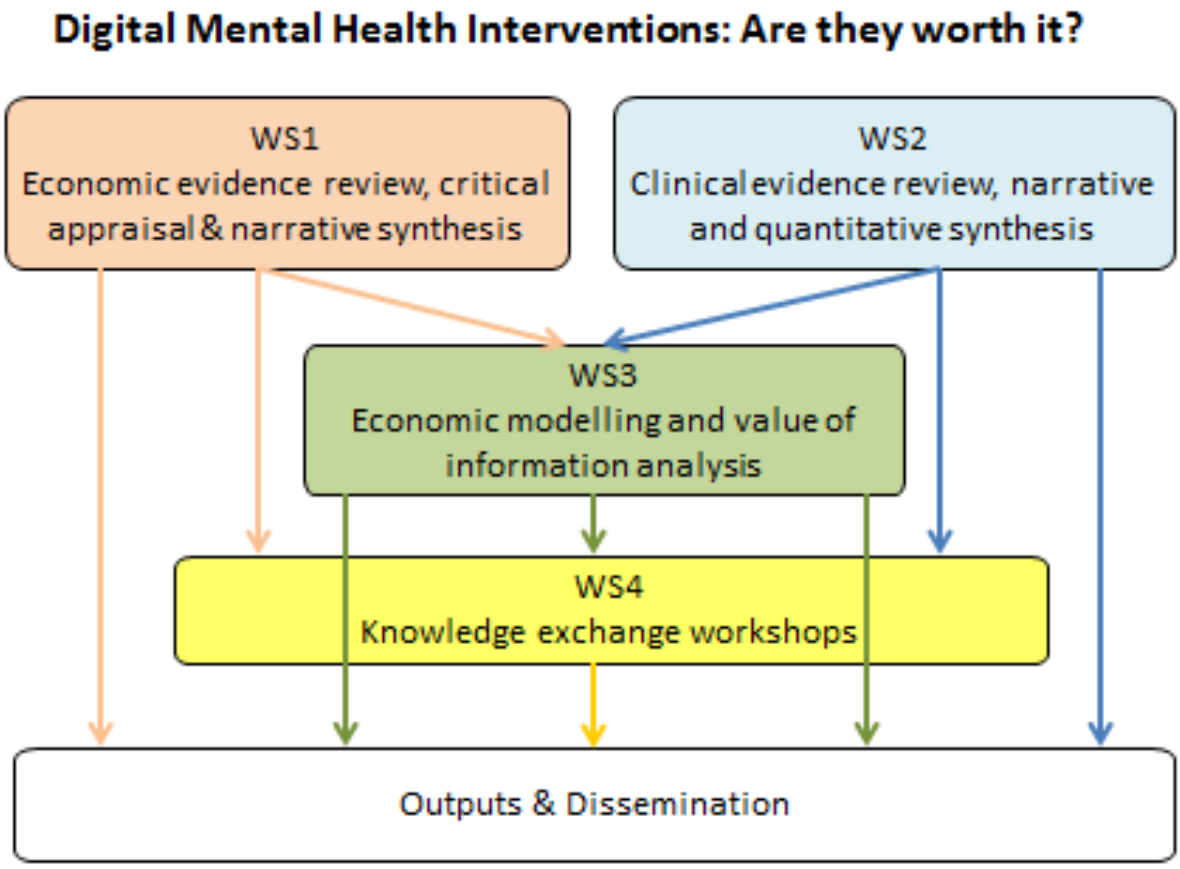
8. To suggest how the methods of future CEAs for DMHIs can be improved by producing a step-by-step guide and a quality assessment checklist.

9. To investigate how the results on CEAs of DMHIs can be most effectively communicated to and inform decision making by:
   a) commissioners to fund services that use DMHIs;
   b) practitioners and service managers to provide DMHIs in routine care;
   c) service users to engage with DMHIs to improve or promote their mental health;
   d) technologists and researchers to further develop and optimise DMHIs.

3. PROJECT DESIGN

The project has 4 work-streams (WS).

- WS1 is a systematic review, critical appraisal and narrative evidence synthesis of all available economic evidence on DMHIs.
- WS2 is a systematic review, narrative synthesis and, when appropriate, quantitative analysis of RCTs and observational studies relating to a sub-set of DMHIs for common mental health problems, where the majority and best quality of clinical evidence exists, but without commensurate economic evidence (few and poor or moderate quality EEs).
- WS3 is the economic modelling and value of information analysis (VoI) for the sub-set of DMHIs for common mental health problems that was reviewed and analysed in WS2.
- WS4 is a series of knowledge exchange workshops with four groups of stakeholders (service users, service providers, commissioners and technologists) to communicate our findings from WSs 1, 2, and 3. The workshops will explore how each stakeholder group may understand, interpret and potentially use these findings and how we can tailor future knowledge exchange activities for each stakeholder group.



4. SEARCH STRATEGY (WS1 and WS2)

We will undertake a comprehensive literature search to identify eligible EEs and eligible clinical studies, mainly RCTs and observational studies, that will are relevant for informing our economic decision model in SW3. The strategy will use mapped terms for each facet of the review topic: (1) digital, (2) mental health intervention, (3) economic evaluation and (4) clinical trial. The search strategy will combine search terms drawn from subject headings (e.g. MESH in Medline) with free-text terms to achieve optimum sensitivity and specificity. This will undergo additional testing prior to being implemented on Medline when the project commences. It will then be adapted for use on the other databases (e.g. translating MeSH terms into Emtree subject headings in Embase). All searches will be designed and run by an experienced information specialist.

The following electronic research databases will be searched: MEDLINE, PreMedline In-Process & Other Non-Indexed Citations (via the Ovid platform), EMBASE (via Ovid); PsycINFO (via EBSCO platform); The Cumulative Index to Nursing and Allied Health Literature (CINAHL) (via EBSCO); Web of Science Core Collection (including the Science Citation Index Expanded and the Social Science Citation Index Expanded); the Cochrane Database of Systematic Reviews (CDSR); the Cochrane Central Register of Controlled Trials (CENTRAL); Database of Abstracts of Reviews of Effectiveness (DARE); NHS Economic Evaluation Database (NHS EED); Health Technology Assessment database and the NIHR Journals Library; Database of promoting health effectiveness reviews (DoPHER).

Database searches will be conducted back to the year 1997, as we know that any relevant EEs of DMHIs could not have been published earlier than this. Searches will be restricted to literature published in the English language, because we anticipate that most reviews and recent studies, even when conducted by non-native English speaking research groups would have a version published in English; e.g. the South Asia Cochrane Group, Hodgins & Peden (2008).

Grey literature (unpublished or non-commercially disseminated) will be sought by searching websites of relevant organisations; e.g. National Institute for Health and Care Excellence (NICE), British Association of Behavioural and Cognitive Psychotherapies (BABCP), King's Fund, Mental Health Foundation. We will also search databases indexing grey literature, such as Opengrey (www.opengrey.eu), which will contain references to potentially relevant theses. Ongoing EEs will also identified, through searches of UK Clinical Trials Gateway (UKCTG), World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), ISRCTN (controlled and other trials) and clinicaltrials.gov. Ongoing SRs will be identified from PROSPERO (international prospective register of systematic reviews) and the Cochrane Library.

Reference lists of studies meeting the inclusion criteria will be checked to identify any additionally relevant EEs. We will also contact researchers in the field and manually search NIHR's portfolio and library to retrieve ongoing economic evaluations. We are aware of important emerging evidence from large NIHR-funded RCTs on digital interventions, e.g. REEACT (Gilbody et al, 2015) and OCTET (Lovell et al, 2017), that have not yet been published but would carry weight for the results of this evidence synthesis.

5. INCLUSION/EXCLUSION OF LITERATURE (WS1 & WS2)

We will use the following inclusion/exclusion criteria, in terms of population, intervention, comparator, outcomes, and design of included research (PICO), to screen and select relevant literature.

1. POPULATION: We will include all populations with symptoms, a history or risk of mental health problems, with consideration for under-represented groups (e.g. learning difficulties).

2. INTERVENTION: We will include all types of interventions for prevention and treatment of mental health problems that involve digital media, both stand-alone interventions and interventions given alongside usual care (e.g. GP consultations, medication). We will pay particular attention to DMHIs that are considered "self-administered" i.e. can be used autonomously by service users.

3. COMPARATORS: We will include comparisons between different types of DMHIs, between DMHIs and non-digital interventions (e.g. using a telephone as a medium for conversation in the remote delivery of therapy without any digital component), and between DMHIs and non-specific interventions (e.g. waiting list or "usual care") and between DMHIs and no intervention.

4. OUTCOMES: Our primary outcome will be the incremental cost-effectiveness ratio for DMHIs vs alternatives, with outcomes expressed as Quality Adjusted Life Years (QALYs) or other consequences (disease specific outcomes or life years). We will focus on mental health related outcomes measured by both generic outcomes (e.g. quality of life, daily functioning, wellbeing, disability) and condition-specific outcomes (e.g. symptoms, risk, recurrence). This will enable us to discuss the generic effects of DMHIs across different populations, as well as the condition-specific effects of DMHIs for each population. We will exclude EEs of DMHIs that report only non-mental health outcomes (e.g. psychological interventions to improve physical health).

We will include EEs published in peer-reviewed journals and EEs that formed part of clinical trials, especially fully-powered randomised controlled trials **comparing DMHIs with non-digital interventions or with no intervention**, that have been completed but not yet published (with the author's permission). We will include EEs that are based on individual trials / studies and EEs that are based on models, although we will summarise these separately. We will only include EEs that consider both costs and outcomes of competing alternatives; cost analyses or budget impact assessments will be excluded from the evidence synthesis, but we will consider them in our broader discussions. We will only include EEs which have assigned monetary values to resources.

The titles and abstracts of all papers identified by the literature search (after duplicates have been removed) will be screened to select potentially relevant EEs. EEs that meet inclusion criteria based on their title or abstract, or EEs for which we cannot make a judgement based on their title and abstract, will be retrieved to assess the full paper. EEs which meet all inclusion criteria will be selected for data extraction and quality assessment.

6. DATA EXTRACTION (WS1 & WS2)

In the first stage, EEs will be grouped according to those relating to clinical studies (trial based or observational) and to modelling studies. For EEs relating to clinical studies, data will be extracted using two bespoke data extraction templates to capture information relating to PICO and to EE design as detailed below. For EEs relating to modelling studies, data will also be extracted using the same data extraction templates (as below), but we will also capture information relating to model structure, synthesis of model data and consistency, including validation checks.

PICO

- Population (participants e.g. age, sex, condition or risk factors, comorbidities, country);
- Intervention (digital and non-digital components);
- Comparator (active intervention component, usual care details, waiting list, etc);
- Outcomes (standardised outcome measures used for the EE, method of data collection e.g. by post, email, app, interview, person completing the measures e.g. patient, carer, professional).

EE design:

- Analytical approach (CMA, CEA, CUA, CBA)
- Perspective (e.g. NHS and PSS/ societal)
- Time horizon of costs.
- Participant flow:
  - N screened for eligibility
  - N lost/excluded pre-randomisation
  - N randomised
  - N completed
  - N lost to follow-up.
- Outcomes (for DMHI and comparator):
  - Time period from baseline to follow-up
  - Baseline score (n, mean, SE or 95% CI),
  - Follow up score (n, mean, SE or 95% CI) for each follow up if multiple points are reported
  - Change in score / incremental effect from baseline to follow-up (n, mean, SE or 95% CI).
- Costs (for DMHI and comparator):
  - Unit cost data (currency & price year)
  - Method used to estimate cost (e.g. per patient costs in trial or description of model)
  - Mean intervention cost (with measures of uncertainty)
  - Mean healthcare cost (with measures of uncertainty)
  - Mean productivity costs (with measures of uncertainty)
  - Mean total costs (with measures of uncertainty)
  - Mean incremental costs for all perspectives reported. (with measures of uncertainty)
- Synthesis of costs and effects:
  - Incremental cost-effectiveness results (for all perspectives, where reported)
  - Discount rate used (for both cost and effect)
  - Methods used to allow for uncertainty e.g. CEAC, sensitivity analyses.

7. QUALITY ASSESSMENT (WS1)

We will assess the quality of the included EEs using an established 10-item quality checklist for EEs (Drummond et al, 2015) and a checklist for modelling studies (Philips, 2006). The Drummond checklist items include 'yes' or 'no' sub-questions (35 in total) each reflecting quality criteria about different aspects of the EE. The Philips good modelling guidance includes a framework focusing on 3 elements of decision analytic modelling - model structure, data and validation - each with a series of questions for critical appraisal.

Across all EEs (individual and modelling studies considered separately), each element of the Drummond/Philips checklists will be taken in turn and the methods utilised in each study will be discussed in terms of their appropriateness for capturing the cost-effectiveness of DMHIs compared to their alternatives. We will make a judgement about the comparative methodological strength of the included studies by inspecting how many of the specified quality criteria are fully met. The methods and data used will also be critiqued in terms of their usefulness for decision making. This critique will follow the principles used in the assessment of evidence submitted as part of technology appraisals for the National Institute for Health and Care Excellence (NICE).

8. DATA SYNTHESIS (WS1 & WS2)

A matrix synthesis will tabulate the key methodological and clinical characteristics, clinical outcomes, cost estimates, HRQoL and cost-effectiveness results of the included EEs. The matrix synthesis will provide a summary estimation of effects and costs, both generic and condition-specific, across a broad range of clinical groups, age groups, and technologies. For example, it may show that certain ICERs based on generic outcomes (e.g. measures of wellbeing and health-related quality of life) are comparable across a number of conditions. The matrix will also identify areas where the quantity and quality of EEs is lacking, and where future studies would be of most value. The matrix synthesis will be accompanied by a narrative description of the key patterns and observations of the assembled EE-level evidence, with due consideration to the methodological quality of the evidence.

We will explore the evidence, from the identified EEs, relating to particular population sub-groups, delivery methods, economic perspectives or outcome measures and conclude on the situations in which the effects and costs of DMHIs may vary. This will also include consideration of why particular DMHIs may not be cost-effective in certain sub-groups or for particular mental health conditions, i.e. what factors are driving the results from published EE's drawing on established criteria (Welte et al, 2004).

Based on the findings of the systematic review on clinical outcomes that were not utilised in primary CEAs, we will conduct a quantitative evidence synthesis using appropriate methods, e.g. fixed effects models. It may also be necessary to utilise methods specific to observational data for some of the model parameters. We will extract data from the clinical effectiveness studies relating to the populations studied, interventions, follow-up times, outcomes, risk of bias, etc. We will use pairwise (meta analysis) and/or network meta-analysis, as appropriate, in order to derive estimates of the clinical effects of relevant digital health technologies (Higgins & Green, 2011; Sutton, Cooper & Jones, 2009). The network meta-analysis approach allows the synthesis of evidence from a number

of studies in which the multiple interventions of interest may not all have been directly compared (Welton et al, 2009). Taking this approach further it is also possible to build a Bayesian "network of evidence" (that enables assessment of findings from competing alternatives simultaneously). Digital mental health intervention effects are likely to be derived via synthesis of any available data from the literature and observational data, where appropriate.

Digital mental health programmes are likely to be based on complex psychological interventions, like Cognitive Behaviour Therapy (CBT), which may include different therapeutic components (e.g. psychoeducation, cognitive techniques, behavioural techniques, motivational interviewing) and different layers of intensity (e.g. high intensity, brief interventions). In addition, digital mental health increasingly follows a blended model in which one intervention may include different types of technologies, e.g. an educational self-help online tool and a monitoring mobile phone app, in combination with different types of personal support, e.g. face-to-face scheduled sessions with a therapist plus standardised texts and emails from an assistant. To help elucidate a taxonomy for categorisation of digital mental health interventions, we will first extract the full details of each intervention based on recommended reporting guidelines (Hoffman et al, 2014; Schulz et al, 2010). At the same time, we will explore the literature to identify those components that influence costs and outcomes, to ensure that these are included in the data extraction (the most notable example being the amount of human support offered as an adjunct to the technology). We will propose classification criteria which are clinically meaningful and evidence-informed to develop a taxonomy framework that can inform the design, replication, cross-study evaluation and implementation of future digital mental health interventions.

9. DECISION MODELLING (WS3)

We will use a decision analytic modelling approach (Briggs, Claxton & Sculpher, 2006) to combine relevant data from WS1 and WS2 so that we can determine the long-term cost-effectiveness and associated uncertainty for specific DMHIs in particular mental health problems, compared to appropriate alternatives. The model will focus on depression and anxiety under the umbrella "common mental health problems". This is because most available and best quality clinical evidence relates to common mental health problems (as opposed to psychosis, eating disorders, autism, etc). Existing systematic reviews and meta-reviews of digital interventions (e.g. Barak et al, 2008; Cuijpers, van Straten & Andersson, 2008; Hollis et al, 2017; Marks, Kavanagh & Gega, 2007; Mayo-Wilson & Montgomery, 2013) demonstrate the volume of clinical studies of DMHIs for mental health problems and the lack of corresponding cost-effectiveness studies for the same.

A group of DMHIs for common mental health problems will be chosen for further modelling on the basis of our critical evaluation of the CEAs relating to these DMHIs. For example, DMHIs will be chosen if the methods or data used to establish their cost-effectiveness in the primary studies were not appropriate, or were flawed, or had omissions, and our critical evaluation deemed it would be appropriate to utilise alternative methods. Modelling will also be appropriate if the primary CEAs of the chosen DMHIs did not utilise a longer-term (lifetime) horizon and our critical appraisal has deemed it appropriate to do so.

The model structure will allow us to develop a clearer understanding of the relationships between incremental costs and consequences of treating common mental health problems. WS1 and WS2

data will enable us to map realistic clinical pathways, so that all relevant options in the decision model(s) are properly represented, all relevant comparators are considered and we include essential data on utilities, costs and other parameters such as adverse events, relapse rates etc.

The perspective of the cost-effectiveness analysis will be the health care service at first, although we will explore the inclusion of non-health care costs, such as productivity changes. Uncertainty in the evidence used to populate the model will be characterised using appropriate distributions and any uncertainty in the adoption decision demonstrated using probabilistic sensitivity analysis (Claxton et al, 2005). We will establish the value of further data collection using value of information analysis (Claxton , 1999) and explore alternative scenarios regarding the extrapolation of our primary outcome over the lifetime of the model. This will be necessary given that many of the studies exploring the effectiveness of DMHIs are likely to be short-term.

10. KNOWLEDGE TRANFER WORKSHOPS (WS4)

Four (4) half-day workshops will be held with groups of stakeholders including:

- commissioners who fund services that use DMHIs;
- practitioners and service managers who provide DMHIs in routine care;
- service users who engage with DMHIs to improve or promote their mental health
- technologists and researchers who further develop and optimise DMHIs.

The workshops will operate within a science communication framework (Bruine de Bruine & Bostrom, 2013; von Winterfeldt, 2013) and will involve the following steps:

a) Listen to the audience to understand the decisions they have to make about DMHIs and the values and intentions that underpin these decisions;
b) Present a summary of our findings in an appropriate way for each stakeholder group and discuss how the group makes sense of the presented information;
c) Understand how the summary of evidence may speak to the values and intentions of stakeholders and how their decisions to invest time and resources in DMHIs may be supported or challenged in view of this evidence;
d) Identify how we can improve understanding and use of economic evidence by stakeholders.

Each workshop will have two parts. The first part will be the communication of our methods and findings through an interactive presentation with case illustrations. The second part will be a structured discussion where we will ask the group to identify the highlights of our findings that were important to them, any aspects of the presentation that were not clear, and offer comments and feedback in general. The discussion part will be audio recorded, so that the narrative data can be transcribed. Using a thematic analysis (Braun and Clarke, 2006), we will identify key themes and draw comparisons about the understanding and potential use of our evidence within and between the different stakeholder groups.

The research team will produce a matrix to map out the themes that emerged from the stakeholder knowledge exchange workshops. In our final expert advisory group meeting, which will include representatives from all stakeholder groups, we will present the findings of the stakeholder workshops and a proposal of how a series of evidence briefings will be structured and communicated to a broad audience.

11. DISSEMINATION AND PROJECTED OUTPUTS

Our project will produce the following outputs:

- The project's protocol, which we will submit for publication.
- A report, which will submit to the NIHR Journals Library (Health Technology Assessment), that details our findings about the cost-effectiveness, uncertainty parameters.
- Three publications in peer reviewed journals (EE review, Clinical Trials Review, Economic Model).
- A step-by-step guide for conducting EEs in DMHIs for non-economists who carry out clinical trials on DMHIs and do not have access to health economics expertise.
- An assessment checklist to help non-economists make judgements about the quality of published EEs of DMHIs.
- A proposal for improving science communication about health economics for different stakeholder groups to help them make sense of cost-effectiveness evidence and inform their decisions in view of this evidence.
- Classification criteria to inform a taxonomy of digital mental health interventions.

Drawing on our two systematic reviews of economic and clinical evidence, on the narrative and quantitative synthesis of the reviewed evidence, on our economic modelling and on the stakeholder workshops, we will produce evidence briefings to help decision makers consider the use of DMHIs within a resource constrained system, such as the UK's NHS. This will include "headline" information such as:

- is a specific DMHI cheaper than its alternatives (yes/no)?
- is a specific DMHI more effective than its alternatives (yes/no)?
- what may influence the DMHI's effectiveness and cost-effectiveness?
- what may influence stakeholder decisions to invest in the DMHI?

We will report our methods and findings of the systematic reviews in accordance with the PRISMA Statements (Moher et al, 2009, 2015). We will report our economic modelling in accordance with the CHEERS statement (Husereau et al, 2013). We will present in scientific and professional conferences. We will disseminate links to the project's publications and summaries of findings via social media e.g. Twitter, Linkedin, the "Mental Elf".

12. PROJECT OVERSIGHT

This is a 18-month project starting 1st Sept 2018 and ending 28th February 2020.

We will set up an expert reference group (ERG) with with 4 PPI representatives and 4 clinicians and academics. The group will meet 6 times throughout 18 months to advise on key methodological issues (e.g. choice of search terms, inclusion/exclusion of literature, taxonomy, challenges with gaps in the literature), and on the presentation, interpretation and dissemination of evidence in different contexts. The role of the ERG will be to ensure that our literature selection is unbiased and inclusive, and that our conclusions and recommendations are justified in view the selected economic evidence and reported in an unambiguous and neutral manner. The ERG meetings will be minuted. Informal communication with the ERG will take place if needed between meetings.

The project will be overseen by an independent Study Steering Committee (SSC) which will include an independent Chair, two independent senior academics and a representative of users and the public, approved and appointed by the NIHR Programme Director. The SSC will meet 3 times every 6 months over the 18 months of the project. The role of the SSC will be to provide advice, through its Chair, to the Project Funder, the Project Sponsor, the Chief Investigator, the Host Institution and the Contractor on all appropriate aspects of the project. The SSC will monitor the progress of the project, adherence to the protocol, and the consideration of new information of relevance to the project's objectives. Meetings will be minuted and the minutes will be sent to all members, the sponsor, and the funder and be retained in the project's master file.

13. APPROVAL BY ETHICS COMMITTEES

Ethics approval is not needed for WS 1, 2 and 3 for which no primary data will be collected. WS 4 will require ethical approval by the University of York and the Health Research Authority (HRA) so that we can record, transcribe and conduct a qualitative analysis of the narrative data collected during the stakeholder knowledge exchange workshops, some of which will involve mental health service users and practitioners. We will ask participants not to disclose personal or family information during the workshops. We will follow a structured topic guide and keep discussions focused on the understanding and potential use of our findings. The project will be subject to the established University of York's Research Management and Governance Arrangements with regards to PPI representation in our advisory group.

14. PATIENT AND PUBLIC INVOLVEMENT

We will include services users and public representatives, alongside other stakeholders such as clinicians and commissioners, throughout our four workstreams (WS). In WS1 and WS2, service user and public representatives, clinicians and academics will take part in consultation groups who will define key parameters and outcomes for our evidence synthesis, thereby guiding the development of the key terms for the literature searches. The information specialists will combine these key terms to develop a draft search strategy and the consultation groups will check the key articles retrieved by this strategy and revise accordingly. The PPI representatives will also review our proposed classification criteria for a taxonomy that categorises digital mental health interventions. In WS3, the consultation groups will help us develop a logic model, i.e. a pre-model structure to define the important events and pathways in our decision model. They will then validate the final model structure and model parameters and they will scrutinise the results and outputs from our decision modelling. WS4 will rely on stakeholder input to co-produce lay audience evidence briefings, develop the topic guides for discussion and interpret the findings from the qualitative data that will emerge from the knowledge exchange workshops and group discussions, make recommendations for use of digital health interventions in services and priorities for future research, and help dissemination via communication with user-led organisations.