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## Study protocol for a systematic review of evidence for digital interventions for co-morbid alcohol use disorder and depression in community-dwelling populations

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## SCHOLARONE™
## Manuscripts

# Study protocol for a systematic review of evidence for digital interventions for co-morbid alcohol use disorder and depression in community-dwelling populations

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## ABSTRACT

**Introduction**

Alcohol use disorder and depression are frequently comorbid and make a substantial contribution to the global non-communicable disease burden.  A range of effective interventions and treatments exist for either AUD or depression alone, including positive emerging evidence base for the use of digital interventions. Computerised and/or smartphone delivered advice could provide flexible, coordinated support for patients co-morbid AUD and depression but to date, no systematic review of the evidence has been conducted. This systematic review will identify and evaluate the effectiveness of digital interventions for reducing co-morbid AUD and depression in community-dwelling populations.

**Methods and analysis**

We will search MEDLINE, The Cochrane Library, CENTRAL, CINAHL, PsycINFO, ERIC and SCI from inception for randomised controlled trials that evaluate any personalised digital intervention for co-morbid alcohol use disorder and depression published in any language. Primary outcomes will be changes in quantity of alcohol consumed and depressive symptoms. Screening, data extraction and risk of bias assessment will be undertaken independently by two reviewers with disagreements resolved through discussion. Meta-analytic methods will be used to synthesise the data collected relating to the primary outcomes of interest.

**Ethics and dissemination**

As being a systematic review, an ethical approval is not needed. Findings will be published in peer-reviewed journals and presented on conferences.

**Keywords:** alcohol use disorders, depression, digital interventions, systematic review, meta-analysis

**Trial registration number**

International Prospective Register for Systematic Reviews (PROSPERO) number:

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**STRENGHTS AND LIMITATIONS**

- To our knowledge, this study represents the first systematic review of digital interventions for comorbid AUD and depression

- This review has the potential to inform the development of evidence-based interventions that could be delivered at scale to this at-risk population

- The strengths of this systematic review include the use of an in-depth search strategy and robust quality appraisal criteria to identify and evaluate the existing literature

- Potential limitations are likely to include between-study heterogeneity of the original studies and publication bias

- Previous research in this field suggests that trials are likely to utilise a range of alcohol consumption and depression measures to assess outcomes

## INTRODUCTION

### Description of the condition

Alcohol and mental health disorders make a substantial contribution to the global non-communicable disease burden [1][2]. Alcohol consumption alone is causally related to over 60 different medical conditions [3], with drinking at hazardous, harmful or dependent levels (alcohol use disorder, or AUD [4]) associated with adverse social and economic consequences that extend beyond the individual drinker to their families, communities and society as a whole [5]. AUD is also highly comorbid with a number of mental health conditions, including lifetime depression [4][6][7]. In the UK, over two-fifths of people presenting with AUD in primary care suffer from depression [8], the majority of people in specialist alcohol treatment services have a co-occurring mental health difficulty [8], and an estimated one in five alcohol-related hospital admissions for mental and behavioural disorders are due to alcohol [9]. Experiencing such conditions co-morbidly is associated with poorer overall outcomes for the individual concerned. AUD is connected with: worsening the depression course, with risks of incident depression higher for heavier as opposed to lighter drinkers [10]; increased suicide risk [11]; and delayed recovery from psychiatric conditions [12].

A range of effective interventions and treatments exist for either AUD or depression alone, including behavioural (typically psychotherapy) delivered either face-to-face or computerised support, and/or pharmacological approaches [13][14]. In mild cases of depression, guided self-help and computerised cognitive behavioural therapy are recommended as initial treatments [15][16]; whilst antidepressant drugs remain the mainstay of treatment for moderate to severe or sustained cases, particularly selective serotonin reuptake inhibitors

[17]. For AUD, there is strong evidence for the effectiveness of brief behavioural advice for

hazardous and harmful alcohol consumption delivered both face-to-face by primary care

clinicians [13], and digitally, via website or smartphone application [18]. Extended interventions

or specialist treatment is recommended for more severe AUD or dependent drinkers [19].

For patients with co-morbid AUD and depression, the picture is more complex. Results for

the use of cognitive-behavioural therapy  and /or motivational interviewing for such

individuals have been promising, demonstrating small but significant effects [20 21]. However

there is limited conclusive evidence concerning whether parallel or integrated treatment

models achieve better treatment outcomes for such patients, particularly over the longer

term [22]. Thus, it is likely that multifaceted, sustained interventions will be needed, delivered

concomitantly, and closely monitored, to optimise their overall impact [23-25]. Given the

positive emerging evidence base for the use of digital interventions with AUD and

depression alone [18 26-32], computerised and/or smartphone delivered advice and support

could support the demand for flexible, more coordinated provision for patients experiencing

such conditions co-morbidly. Several trials suggest positive outcomes for digital

interventions for co-morbid AUD and depression [33-37], but to date, no systematic review of

the evidence has been conducted. The proposed review aims to assess the effectiveness of

digital interventions for reducing co-morbid hazardous and harmful alcohol consumption

and mild to moderate depression in community-dwelling populations.

**METHODS AND ANALYSIS**

This systematic review is registered with the International Prospective Register of

Systematic Reviews (PROSPERO, https://www.crd.york.ac.uk/PROSPERO, registration

number: CRD42019130134). The protocol has been written according to the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses-Protocol (PRISMA-P)

recommendations [38] and the findings will be reported using PRISMA guidelines [39].

**Criteria for study inclusion**

Population: studies must be performed among community-dwelling adults (18 years and

older) who have personally sought out or been directed towards any digital intervention for

co-morbid alcohol use disorder and depression. Participants must be must be identified by

themselves, significant others or via a validated screening process as having co-morbid

alcohol use disorder and depression. Alcohol-use disorders cover a wide range of mental

health problems as recognised within the international disease classification systems (ICD-

10, DSM-IV). These include hazardous drinking (a pattern of alcohol consumption that

increases someone's risk of harm), harmful drinking (a pattern of alcohol consumption that

is causing mental or physical damage (ICD-10, DSM-V)) and alcohol dependence (a cluster of

behavioural, cognitive and physiological factors that typically include a strong desire to drink

alcohol and difficulties in controlling its use). Depression is defined as either depression

disorder or clinical depression assessed according to the Diagnostic and Statistical Manual of

Mental Disorders (DSM) or International Classification of Diseases (ICD) by a standardized

interview (e.g. Structured Clinical Interview, Composite International Diagnostic Interview)

or via validated self-reports or rating scales with specific cut-off points for depression.

Studies will be excluded if they are directed mainly towards people who are seeking

specialist health or social care treatment for their alcohol consumption and depression, or if

they deliver the intervention in a secondary or tertiary care setting.

Intervention: must be digital, defined as being delivered primarily through a programmable

computer or mobile device (laptop, phone, or tablet), including web-based, mobile phone

text messaging, smart-phone applications, social networking, or 'stand-alone' computer-based technologies (CD-ROMs) and must respond to user input and generate personalised content which aims to address the participants' alcohol-related behaviours and depression. Interventions which do not generate feedback or other output based on the personal characteristics of the user will not be included (for example, generic educational interventions). Interventions are not restricted to those accessible online.

Comparator condition: may be no intervention, usual care (in a health or social care setting), or other digital or face to face brief intervention to reduce alcohol consumption and depression.

Outcomes: the primary outcomes will be: (1) quantity of alcohol consumed, which may be reported in standard drinks, alcohol units or similar, and which we will convert into grams of alcohol; (2) change in depressive symptoms, measured by a standardised or validated measure (Beck Depression Inventory [40]; Hamilton Depression Rating Scale [41], Patient Health Questionnaire [42], Depression Anxiety Stress Scales [43], or any other depression scale). Secondary outcomes include: number of binge episodes; frequency of drinking occasions; quality of life (measured by the A. Short Form Health Survey [44] or other validated tool); . behaviour (measured by deaths by suicide, suicide attempts, episodes of deliberate self-harm [45]); and any reported adverse effects.

Setting: Participants may be recruited in a range of settings, including primary health care (including emergency departments), social care, educational, workplace or community, and there is no restriction on where participants may interact with the intervention, given that it may be delivered through mobile devices.

Study type: Only randomised controlled trials, with individual, cluster, stepped wedge and n-of 1 designs, will be eligible for inclusion. We will exclude cross-sectional studies, case series and case reports.

**Search strategy for identification of studies**

We will search the following electronic databases from inception to identify studies for inclusion in the review: MEDLINE (Ovid); The Cochrane Library (Wiley); CENTRAL (Cochrane Central Register of Controlled Trials); CINAHL (EBSCO); PsycINFO (Ovid); ERIC (EBSCO); and SCI (Science Citation Index via Web of Knowledge). Additionally, potentially eligible studies included in the recent Cochrane Review of Personalised digital interventions for reducing hazardous and harmful alcohol consumption [18] will be identified from electronic databases held by the authors. We will check reference lists of all included studies and other relevant reviews, carry out citation searches for included studies, and consult experts to confirm nothing has been missed. The search will not be limited by publication status, language or date. An example of the proposed search strategy for MEDLINE is outlined in Table 1.

***Table 1: MEDLINE search strategy***

| # | Searches |
|---|----------|
| 1 | exp Alcohol-Related Disorders/ |
| 2 | exp Alcohol Drinking/ |
| 3 | (alcohol$ adj2 (drink$ or intoxicat$ or use$ or abus$ or misus$ or risk$ or consum$ or withdraw$ or detox$ or treat$ or therap$ or excess$ or reduc$ or cessation or intervention$)).tw. |
| 4 | (drink$ adj2 (excess or heavy or heavily or harm or harmful or hazard$ or binge or harmful or problem$)).tw. |
| 5 | ("alcohol use" or alcoholic$).tw. |
| 6 | or/1-5 |
| 7 | Depression/ |
| 8 | exp Depressive Disorder/ |
| 9 | Mood Disorders/ |
| 10 | dysthymi$.tw. |
| 11 | (depressi$ adj3 disorder$).tw. |
| 12 | (depressi$ adj3 symptom$).tw. |

| 13 | mood disorder$.tw. |
|----|-----|
| 14 | affective disorder$.tw. |
| 15 | antidepress$.tw. |
| 16 | anti-depress$.tw. |
| 17 | or/7-16 |
| 18 | Internet/ |
| 19 | Blogging/ |
| 20 | Social Media/ |
| 21 | Computers/ |
| 22 | exp Microcomputers/ |
| 23 | Minicomputers/ |
| 24 | Therapy, Computer-Assisted/ |
| 25 | Computer-Assisted Instruction/ |
| 26 | exp Cellular Phone/ |
| 27 | Electronic Mail/ |
| 28 | ((email$ or e-mail$ or electronic mail$ or text messag$ or SMS or MMS or phone? or cellphone? or cell-phone? or smartphone? or smart-phone? or digital tablet? or pda or personal digital assistant? or social media or social networking or facebook or twitter or skyp$ or app?) adj3 (deliver$ or generat$ or based or provid$ or facilitat$ or support$ or treatment? or therap$ or intervention? or program$ or feedback)).ti,ab. |
| 29 | ((Internet$ or electronic$ or digital$ or technolog$ or online or on-line or computer$ or laptop? or software or web$ or weblog$ or blog$ or CD? or CD-ROM?) adj3 (deliver$ or generat$ or based or provid$ or facilitat$ or support$ or treatment? or therap$ or intervention? or program$ or feedback)).ti,ab. |
| 30 | (e-BI or e-SBI or ehealth or e-health or electronic health or mhealth or m-health or mobile health or virtual health or digital health or technological aid?).ti,ab. |
| 31 | or/18-30 |
| 32 | 6 and 17 and 31 |
| 33 | randomized controlled trial.pt. |
| 34 | controlled clinical trial.pt. |
| 35 | randomi*.ab. |
| 36 | placebo.ab. |
| 37 | drug therapy.fs. |
| 38 | randomly.ab. |
| 39 | trial.ab. |
| 40 | groups.ab. |
| 41 | 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 |
| 42 | (animals not (humans and animals)).sh. |
| 43 | 41 not 42 |
| 44 | 32 and 43 |

**Study selection process**

Following de-duplication of the search results, two researchers will independently screen all

titles and abstracts identified, using Endnote to ensure consistency in screening approach.

The full research papers of any studies identified as being potentially eligible will be

reviewed by two researchers independently. Any discrepancies will be resolved by

discussion and by consulting a third researcher if necessary to reach consensus. Reasons for

exclusion from this phase of the search will be recorded. A PRISMA flow chart will outline

the study selection process and reasons for exclusions.

**Data extraction**

Data will be extracted using a standardised data extraction form specifically developed and

piloted for this study. Extracted data will include: study design and setting; sample size

including recruitment and retention rates; participant characteristics; details of the

intervention (including mode of delivery); primary and secondary outcome measures

(including standard deviations or related measures of variability) and information for the

assessment of the risk of bias. Two researchers will carry out data extraction of each

included study independently, with any discrepancies resolved by a third researcher. Where

multiple eligible outcomes are recorded for depression, we will prioritise data from rating

scales (eg Hamilton Rating Scale for Depression) over self-report questionnaires (eg Beck

Depression Inventory).

**Risk of bias**

Two researchers will independently assess the risk of bias of the included studies using the

Cochrane Collaboration's tool for assessing risk of bias in RCTs [46]. For each included RCT, we

will provide a description, comment and judgement of risk of bias for the following items:

(1) bias arising from the randomization process; (2) bias due to deviations from intended

interventions; (3) bias due to missing outcome data; (4) bias in measurement of the

outcome; and (5) bias in selection of the reported result (see Appendix 1 for details). These

judgments will be informed by the criteria adapted to the addiction field by the Cochrane

Collaboration. Blinding of participants, personnel and outcome assessor (avoidance of

performance bias and detection bias) will be considered separately for objective outcomes

(e.g. drop out, use of substance of abuse measured by urine analysis, subjects relapsed at

the end of follow-up, subjects engaged in further treatments) and subjective outcomes (e.g.

duration and severity of signs and symptoms of withdrawal, patient self-reported use of

substance, side effects, social functioning as integration at school or at work, family

relationship). Incomplete outcome data (avoidance of attrition bias) will be considered for

all outcomes except for the drop out from the treatment, which is very often the primary

outcome measure in trials on addiction.

**Synthesis of data and summary measures**

<u>Data synthesis and meta-analysis</u>

For all included RCTs, we will provide a detailed description of the results in both tables and

text. If studies are sufficiently homogeneous to enable meta-analysis, we will pool the data

for each outcome using a random-effects model in a meta-analysis that compares

intervention and control arms, using mean differences or standardized mean differences as

appropriate for continuous variables and relative risks for dichotomous outcomes. The

meta-analysis will be performed using RevMan V5.3. If meta-analysis is not feasible, we will

carry out a narrative summary of studies.

In the outcome assessment, for continuous variable outcomes (e.g. quantity of alcohol

consumed or scores in depression scales) we will compare standardized mean differences

(SMD). For dichotomous outcomes (e.g. participants classified as drinking over set limits or

having depression remission), we will compare proportions using risk ratios. Where

outcomes have been assessed at more than one time, data for each time point will be

extracted. Depending on the availability of sufficient data, we will analyse follow-up

durations using different time frames: 1) short term (up to six months post-intervention); 2)

medium term (6-12 months post-intervention); and 3) long-term (more than 12 months

post-intervention).

Unit of analysis issues

For trials with more than one - and very similar - control or treatment arms, the results for

these arms will be combined in the meta-analysis. If study arms cannot be combined, e.g.

due to important differences in intervention characteristics, each pair-wise comparison will

be included separately. To avoid the multiple use of participants in the pooled estimate of

treatment effect, every arm that is included more than once, will be divided by the number

of comparisons where it is included.

For dichotomous outcomes, both the total number of patients and the number of events

and will be divided up. For continuous outcomes, the means and standard deviations will be

left unchanged, and only the total number of participants will be divided. This method

retains information from each arm of the trial while it compromises the precision of the

pooled estimate slightly.

To allow the inclusion of cluster randomised trials with individually randomised trials in the

same meta-analysis, we need to account for the relative variability within and between

clusters. If a trial report only contains data that is not adjusted for the cluster design, we will

add an external estimate of the intra-cluster coefficient (ICC) to estimate a design effect,

thus inflating the variance of the effect estimate.

Dealing with missing data

We will contact authors to try to obtain missing data. Where this is impossible, we will attempt to estimate primary outcome measures using secondary outcome measures; for example, estimating quantity of alcohol consumed using frequency and intensity of consumption. Trials with missing standard deviations will be excluded from the main analysis for the associated continuous measure, but may be included in a sensitivity analysis, using imputed values for the standard deviations.

Assessment of heterogeneity

Statistical heterogeneity will be assessed for significance with the Cochran's Q test statistic, and quantified with the $I^2$ value [47]. Causes of heterogeneity will be explored both narratively and using subgroup and sensitivity analyses.

Assessment of publication bias

We will evaluate publication bias using the Egger test and funnel plots [48].

Sensitivity analysis

We will conduct sensitivity analyses by investigating the effect of restricting to studies with a low overall risk of bias.

**Patient and Public Involvement**

Patients and the public were not involved in the design and will be not involved in the conduction of the review.

**ETHICS AND DISSEMINATION**

As no primary data from studies will be collected, an ethical approval is not needed for this systematic review. Findings will be published in peer-reviewed journals and presented on scientific conferences, congresses and symposia.

**CONCLUSION**

This review will examine the effectiveness of digital interventions for comorbid AUD and depression. Digital interventions, delivered via computer or mobile phone, have the potential to provide cost-effective support for patients with AUD and depression who may otherwise face socio-economic and structural barriers to treatment. However, whilst previous studies have synthesised evidence of the impact of digital interventions on AUD or depression alone, there is no comprehensive review that considers the effectiveness of such interventions in comorbid populations. This review will respond to this knowledge gap, and thus has the potential to inform the development of evidence-based interventions that could be delivered at scale to this at-risk population.

The strengths of this systematic review include the use of an in-depth search strategy and robust quality appraisal criteria to identify and evaluate the existing literature. However potential limitations are likely to include between-study heterogeneity of the original studies and publication bias. Previous research in this field suggests that trials are likely to utilise a range of alcohol consumption and depression measures to assess outcomes [49]. Further, whilst we will endeavour to retrieve data from eligible unpublished and non-significant studies, our findings could be limited by publication bias [50].

In conclusion, to our knowledge, this study represents the first systematic review of interventions for comorbid AUD and depression. Findings will have relevance for healthcare practitioners and policy-makers, as well as helping to inform the direction of future research in this field.

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**Patient consent:** Not required.

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**Appendix 1: Revised Cochrane risk-of-bias tool for randomised trials (RoB 2.0)**

## Domain 1: Risk of bias arising from the randomization process

| Signalling questions | Description | Response options |
|---|---|---|
| 1.1 Was the allocation sequence random? | | Y / PY / PN / N / NI |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | Y / PY / PN / N / NI |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** | | **Low / High / Some concerns** |
| Optional: What is the predicted direction of bias arising from the randomization process? | | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

## Domain 2: Risk of bias due to deviations from the intended interventions

| Signalling questions | Description | Response options |
|---|---|---|
| 2.1. Were participants aware of their assigned intervention during the trial? | | Y / PY / PN / N / NI |
| 2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | Y / PY / PN / N / NI |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | NA / Y / PY / PN / N / NI |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | | NA / Y / PY / PN / N / NI |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA / Y / PY / PN / N / NI |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | Y / PY / PN / N / NI |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | NA / Y / PY / PN / N / NI |

| | | |
|---|---|---|
| **Risk-of-bias judgement** | | **Low / High / Some concerns** |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? | | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 2: Risk of bias due to deviations from the intended interventions

| Signalling questions | Description | Response options |
|---|---|---|
| 2.1. Were participants aware of their assigned intervention during the trial? | | Y / PY / PN / N / NI |
| 2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | Y / PY / PN / N / NI |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups? | | NA / Y / PY / PN / N / NI |
| 2.4. Could failures in implementing the intervention have affected the outcome? | | Y / PY / PN / N / NI |
| 2.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** | | **Low / High / Some concerns** |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? | | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 3: Missing outcome data

| Signalling questions | Description | Response options |
|---|---|---|
| 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | Y / PY / PN / N / NI |
| 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | | NA / Y / PY / PN / N |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | | NA / Y / PY / PN / N / NI |
| 3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups? | | NA / Y / PY / PN / N / NI |

| | | |
|---|---|---|
| 3.5 <u>If Y/PY/NI to 3.3</u>: Is it likely that missingness in the outcome depended on its true value? | | NA / Y / PY / <u>PN</u> / <u>N</u> / NI |
| **Risk-of-bias judgement** | | **Low / High / Some concerns** |
| Optional: What is the predicted direction of bias due to missing outcome data? | | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 4: Risk of bias in measurement of the outcome

| Signalling questions | Description | Response options |
|---|---|---|
| 4.1 Was the method of measuring the outcome inappropriate? | | Y / PY / <u>PN</u> / <u>N</u> / NI |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ? | | Y / PY / <u>PN</u> / <u>N</u> / NI |
| 4.3 <u>If N/PN/NI to 4.1 and 4.2</u>: Were outcome assessors aware of the intervention received by study participants ? | | Y / PY / <u>PN</u> / <u>N</u> / NI |
| 4.4 <u>If Y/PY/NI to 4.3</u>: Could assessment of the outcome have been influenced by knowledge of intervention received? | | NA / Y / PY / <u>PN</u> / <u>N</u> / NI |
| 4.5 <u>If Y/PY/NI to 4.4</u>: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA / Y / PY / <u>PN</u> / <u>N</u> / NI |
| **Risk-of-bias judgement** | | **Low / High / Some concerns** |
| Optional: What is the predicted direction of bias in measurement of the outcome? | | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 5: Risk of bias in selection of the reported result

| Signalling questions | Description | Response options |
|---|---|---|
| 5.1 Was the trial analysed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis ? | | <u>Y</u> / <u>PY</u> / PN / N / NI |
| Is the numerical result being assessed likely to have been selected, on the basis of the results, from... | | |

| 5.2. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | Y / PY / PN / N / NI |
|---|---|---|
| 5.3 ... multiple analyses of the data? | | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** | | **Low / High / Some concerns** |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Overall risk of bias

| **Risk-of-bias judgement** | | **Low / High / Some concerns** |
|---|---|---|
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

| Section and topic | Item No |
|---|---|
| **ADMINISTRATIVE** | |
| Title: | |
|    Identification | 1a |
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| Authors: | |
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| **INTRODUCTION** | |
| Rationale | 6 |
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| Eligibility criteria | 8 |
| Information sources | 9 |
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| Study records: | |
|    Data management | 11a |
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| | 15b |
| | 15c |

|  | 15d |
| --- | --- |
| Meta-bias(es) | 16 |
| Confidence in cumulative evidence | 17 |

**Checklist item**

Identify the report as a protocol of a systematic review

If the protocol is for an update of a previous systematic review, identify as such

If registered, provide the name of the registry (such as PROSPERO) and registration number

Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author

Describe contributions of protocol authors and identify the guarantor of the review

If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments

Indicate sources of financial or other support for the review

Provide name for the review funder and/or sponsor

Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the

Describe the rationale for the review in the context of what is already known

Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)

Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review

Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage

Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated

Describe the mechanism(s) that will be used to manage records and data throughout the

State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in

Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from

List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications

List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale

Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis

Describe criteria under which study data will be quantitatively synthesised

If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's τ)

Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)

If quantitative synthesis is not appropriate, describe the type of summary planned

Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)

Describe how the strength of the body of evidence will be assessed (such as GRADE)

**Page Number**

Title, p. 1

n/a

Prospero Registration number: CRD42019130134, p. 3

p.1

p. 21

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Funding sources, p. 21

n/a

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p. 13

Studies will be assessed by using various tools and tests. Revised Cochrane risk-of-bias tool for randomised trials (RoB 2.0), p. 10 pp. 21-25; Cochran's Q test statistic (p. 13), PICO (pp. 6-8), Egger test, funnel plots p.13 and by statitical analyses to assess imprecision (effect size estimates) and heterogenity (p.13)

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# Study protocol for a systematic review of evidence for digital interventions for co-morbid excessive drinking and depression in community-dwelling populations

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# Study protocol for a systematic review of evidence for digital interventions for co-morbid excessive drinking and depression in community-dwelling populations

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1　**ABSTRACT**

2　**Introduction**

3　Excessive drinking and depression are frequently comorbid and make a substantial

4　contribution to the global non-communicable disease burden. A range of effective

5　interventions and treatments exist for either excessive drinking or depression alone,

6　including positive emerging evidence base for the use of digital interventions. Computerised

7　and/or smartphone delivered advice could provide flexible, coordinated support for patients

8　with co-morbid excessive drinking and depression. However to date, no systematic review

9　of the evidence has been conducted focused on the effectiveness of digital interventions for

10　this specific comorbid population. This systematic review will identify and evaluate the

11　effectiveness of digital interventions for reducing co-morbid excessive drinking and

12　depression in community-dwelling populations.

13　**Methods and analysis**

14　We will search MEDLINE, The Cochrane Library, CENTRAL, CINAHL, PsycINFO, ERIC and SCI

15　from inception to end July 2019 for randomised controlled trials that evaluate any

16　personalised digital intervention for co-morbid excessive drinking and depression published

17　in any language. Primary outcomes will be changes in quantity of alcohol consumed and

18　depressive symptoms. Screening, data extraction and risk of bias assessment will be

19　undertaken independently by two reviewers with disagreements resolved through

20　discussion. Meta-analytic methods will be used to synthesise the data collected relating to

21　the primary outcomes of interest.

22　**Ethics and dissemination**

1

As being a systematic review, an ethical approval is not needed. Findings will be published in peer-reviewed journals and presented on conferences.

2

3 **Keywords:** alcohol use disorders, excessive drinking, depression, digital interventions, systematic review, meta-analysis**.**

4

5 **Trial registration number**

6 International Prospective Register for Systematic Reviews (PROSPERO) number: CRD42019130134

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9 **STRENGHTS AND LIMITATIONS**

10 • To our knowledge, this study represents the first systematic review focussed specifically on the effectiveness of digital interventions for comorbid excessive drinking and depression.

• This review has the potential to inform the development of evidence-based interventions that could be delivered at scale to this at-risk population.

• The strengths of this systematic review include the use of an in-depth search strategy and robust quality appraisal criteria to identify and evaluate the existing literature.

• Potential limitations are likely to include between-study heterogeneity of the original studies and publication bias.

• Previous research in this field suggests that trials are likely to utilise a range of alcohol consumption and depression measures to assess outcomes

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1    **INTRODUCTION**

2    **Description of the condition**

3    Alcohol and mental health disorders make a substantial contribution to the global non-

4    communicable disease burden (1, 2). Alcohol consumption alone is causally related to over

5    60 different medical conditions (3), with excessive drinking associated with adverse social

6    and economic consequences that extend beyond the individual drinker to their families,

7    communities and society as a whole (4). Excessive drinking is defined here as either

8    hazardous drinking, a pattern of alcohol consumption that increases an individual's risk of

9    harmful consequences (5), or harmful drinking, a pattern that is causing mental or physical

10   damage (6, 7). Excessive drinking is highly comorbid with a number of mental health

11   conditions, including lifetime depression (8-10). In the United Kingdom, over two-fifths of

12   people presenting with excessive drinking in primary care suffer from depression (11), and

13   an estimated one in five hospital admissions for mental and behavioural disorders are due

14   to alcohol (12). Experiencing such conditions co-morbidly is associated with poorer overall

15   outcomes for the individual concerned. Excessive drinking is connected with: worsening the

16   depression course, with risks of incident depression higher for heavier as opposed to lighter

17   drinkers (13), increased suicide risk (14), and delayed recovery from psychiatric conditions

18   (15).

19   A range of effective interventions and treatments exist for either excessive drinking or

20   depression alone, including behavioural (typically psychotherapy) delivered either face-to-

21   face or computerised support, and/or pharmacological approaches (16, 17). In mild cases of

22   depression, guided self-help and computerised cognitive behavioural therapy are

23   recommended as initial treatments (18, 19); whilst antidepressant drugs remain the

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1    mainstay of treatment for moderate to severe or sustained cases, particularly selective

2    serotonin reuptake inhibitors (20). For excessive drinking, there is strong evidence for the

3    effectiveness of brief behavioural advice for hazardous and harmful alcohol consumption

4    delivered both face-to-face by primary care clinicians (16), and digitally, via website or

5    smartphone application (21). Specialist treatment is recommended for those drinking at

6    dependent levels (22).

7    For patients with co-morbid excessive drinking and depression, the picture is more complex.

8    Results for the use of cognitive-behavioural therapy and /or motivational interviewing for

9    such individuals have been promising, demonstrating small but significant effects (23, 24).

10   However there is limited conclusive evidence concerning whether parallel or integrated

11   treatment models achieve better treatment outcomes for such patients, particularly over

12   the longer term (25). Thus, it is likely that multifaceted, sustained interventions will be

13   needed, delivered concomitantly, and closely monitored, to optimise their overall impact

14   (26-28). Given the positive emerging evidence base for the use of digital interventions with

15   excessive drinking and depression alone (21, 29-35), computerised and/or smartphone

16   delivered advice and support could support the demand for flexible, more coordinated

17   provision for patients experiencing such conditions co-morbidly. Several trials suggest

18   positive outcomes for digital interventions for co-morbid excessive drinking and depression

19   (36-40), but to date, no systematic review of the evidence has been conducted focussed on

20   this specific comorbid population. The proposed review aims to assess the effectiveness of

21   digital interventions for reducing co-morbid hazardous and harmful alcohol consumption

22   and mild to moderate depression in community-dwelling populations.

1 **METHODS AND ANALYSIS**

2 This systematic review is registered with the International Prospective Register of

3 Systematic Reviews (PROSPERO, https://www.crd.york.ac.uk/PROSPERO, registration

4 number: CRD42019130134). The protocol has been written according to the Preferred

5 Reporting Items for Systematic Reviews and Meta-Analyses-Protocol (PRISMA-P)

6 recommendations (41) and the findings will be reported using PRISMA guidelines (42).

7 **Criteria for study inclusion**

8 Population: Studies must be performed among community-dwelling adults (18 years and

9 older), who have been identified by themselves, significant others or via a validated

10 screening process as having co-morbid excessive drinking and depression, and have

11 personally sought out or been directed towards any digital intervention for co-morbid

12 excessive drinking and depression. Excessive drinking is defined here as either hazardous or

13 harmful drinking (5-7). Depression is defined as either major depression disorder, persistent

14 depressive disorder or clinical depression assessed according to the World Health

15 Organisation (WHO) ICD-10 classification of mental and behavioural disorders ICD-10 (7) or

16 the Diagnostic and Statistical Manual of Mental Disorders (DSM–5) (6) by a standardized

17 interview (e.g. Structured Clinical Interview, Composite International Diagnostic Interview)

18 or via validated self-reports or rating scales with specific cut-off points for depression.

19 Studies will be excluded if interventions are directed mainly towards people who are

20 seeking specialist health or social care for alcohol dependence and/or severe depression

21 (such as in-patient/residential programmes), or who were in treatment for, or recovery

22 from, alcohol dependence (e.g. 12-step programmes).

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1   Intervention: Must be digital, defined as being delivered primarily through a programmable

2   computer or mobile device (laptop, phone, or tablet), including web-based, mobile phone

3   text messaging, smart-phone applications, social networking, or 'stand-alone' computer-

4   based technologies (CD-ROMs) and must respond to user input and generate personalised

5   content which aims to address the participants' alcohol-related behaviours and depression.

6   Interventions which do not generate feedback or other output based on the personal

7   characteristics of the user will not be included (for example, generic educational

8   interventions). Interventions are not restricted to those accessible online.

9   Comparator condition: No intervention, usual care (in a health or social care setting), or

10  other digital or face to face brief intervention to reduce alcohol consumption and

11  depression.

12  Outcomes: The primary outcomes will be: (1) quantity of alcohol consumed, which may be

13  reported in standard drinks, alcohol units or similar, and which we will convert into grams of

14  alcohol; (2) change in depressive symptoms, measured by a standardised or validated

15  measure (Beck Depression Inventory (BDI) (43); Hamilton Depression Rating Scale (HAM-D)

16  (44), Patient Health Questionnaire (45), Depression Anxiety Stress Scales (46), or any other

17  depression scale). Where studies employ multiple validated rating scales for depression,

18  preference would be for the BDI as a self-rating scale and for the HAM-D as an

19  observer-rating scale (47). In acknowledgment of the varied outcome measures currently

20  employed in these fields (48, 49), we will also include the following secondary outcomes of

21  relevance: number of drinking days; number of heavy drinking days; number of drinks per

22  drinking day; number of days abstinent; total abstinence; time to relapse; quality of life

23  (measured by the 36-item Short Form Health Survey (50) or other validated tool);

1    suicide-related behaviour (measured by deaths by suicide, suicide attempts, episodes of

2    deliberate self-harm (51)); and any reported adverse effects. To be eligible for inclusion,

3    studies must report outcomes for both alcohol consumption and depression symptoms.

4    <u>Setting</u>: Participants may be recruited in a range of settings, including primary health care

5    (including emergency departments), social care, educational, workplace or community.

6    There is no restriction on where participants may interact with the intervention, given that it

7    may be delivered through mobile devices.

8    <u>Study type</u>: Only randomised controlled trials, with individual, cluster, stepped wedge and n-

9    of 1 designs, will be eligible for inclusion. We will exclude cross-sectional studies, case series

10    and case reports.

11    **Search strategy for identification of studies**

12    We will search the following electronic databases from inception to identify studies for

13    inclusion in the review: MEDLINE (Ovid); The Cochrane Library (Wiley); CENTRAL (Cochrane

14    Central Register of Controlled Trials); CINAHL (EBSCO); PsycINFO (Ovid); ERIC (EBSCO); and

15    SCI (Science Citation Index via Web of Knowledge). Additionally, potentially eligible studies

16    included in the recent Cochrane Review of Personalised digital interventions for reducing

17    hazardous and harmful alcohol consumption (21) will be identified from electronic

18    databases held by the authors. We will check reference lists of all included studies and other

19    relevant reviews, carry out citation searches for included studies, and consult experts to

20    confirm nothing has been missed. The search will not be limited by publication status,

21    language or date. An example of the proposed search strategy for MEDLINE is outlined in

22    <u>Table 1</u>.

23    *Table 1: MEDLINE search strategy*

| # | Searches |
|---|---|
| **1** | exp Alcohol-Related Disorders/ |
| **2** | exp Alcohol Drinking/ |
| **3** | (alcohol$ adj2 (drink$ or intoxicat$ or use$ or abus$ or misus$ or risk$ or consum$ or withdraw$ or detox$ or treat$ or therap$ or excess$ or reduc$ or cessation or intervention$)).tw. |
| **4** | (drink$ adj2 (excess or heavy or heavily or harm or harmful or hazard$ or binge or harmful or problem$)).tw. |
| **5** | ("alcohol use" or alcoholic$).tw. |
| **6** | or/1-5 |
| **7** | Depression/ |
| **8** | exp Depressive Disorder/ |
| **9** | Mood Disorders/ |
| **10** | dysthymi$.tw. |
| **11** | (depressi$ adj3 disorder$).tw. |
| **12** | (depressi$ adj3 symptom$).tw. |
| **13** | mood disorder$.tw. |
| **14** | affective disorder$.tw. |
| **15** | antidepress$.tw. |
| **16** | anti-depress$.tw. |
| **17** | or/7-16 |
| **18** | Internet/ |
| **19** | Blogging/ |
| **20** | Social Media/ |
| **21** | Computers/ |
| **22** | exp Microcomputers/ |
| **23** | Minicomputers/ |
| **24** | Therapy, Computer-Assisted/ |
| **25** | Computer-Assisted Instruction/ |
| **26** | exp Cellular Phone/ |
| **27** | Electronic Mail/ |
| **28** | ((email$ or e-mail$ or electronic mail$ or text messag$ or SMS or MMS or phone? or cellphone? or cell-phone? or smartphone? or smart-phone? or digital tablet? or pda or personal digital assistant? or social media or social networking or facebook or twitter or skyp$ or app?) adj3 (deliver$ or generat$ or based or provid$ or facilitat$ or support$ or treatment? or therap$ or intervention? or program$ or feedback)).ti,ab. |
| **29** | ((Internet$ or electronic$ or digital$ or technolog$ or online or on-line or computer$ or laptop? or software or web$ or weblog$ or blog$ or CD? or CD-ROM?) adj3 (deliver$ or generat$ or based or provid$ or facilitat$ or support$ or treatment? or therap$ or intervention? or program$ or feedback)).ti,ab. |
| **30** | (e-BI or e-SBI or ehealth or e-health or electronic health or mhealth or m-health or mobile health or virtual health or digital health or technological aid?).ti,ab. |
| **31** | or/18-30 |
| **32** | 6 and 17 and 31 |
| **33** | randomized controlled trial.pt. |

| 34 | controlled clinical trial.pt. |
|----|------------------------------|
| 35 | randomi*.ab. |
| 36 | placebo.ab. |
| 37 | drug therapy.fs. |
| 38 | randomly.ab. |
| 39 | trial.ab. |
| 40 | groups.ab. |
| 41 | 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 |
| 42 | (animals not (humans and animals)).sh. |
| 43 | 41 not 42 |
| 44 | 32 and 43 |

1  **Study selection process**

2  Following de-duplication of the search results, two researchers will independently screen all

3  titles and abstracts identified, using Endnote to ensure consistency in screening approach.

4  The full research papers of any studies identified as being potentially eligible will be

5  reviewed by two researchers independently. Any discrepancies will be resolved by

6  discussion and by consulting a third researcher if necessary to reach consensus. Reasons for

7  exclusion from this phase of the search will be recorded. A PRISMA flow chart will outline

8  the study selection process and reasons for exclusions.

9  **Data extraction**

10 Data will be extracted using a standardised data extraction form specifically developed and

11 piloted for this study. Extracted data will include: study design and setting; sample size

12 including recruitment and retention rates; participant characteristics; details of the

13 intervention (including mode of delivery); primary and secondary outcome measures

14 (including standard deviations or related measures of variability) and information for the

15 assessment of the risk of bias. Two researchers will carry out data extraction of each

16 included study independently, with any discrepancies resolved by a third researcher. Where

17 multiple eligible outcomes are recorded for depression, we will prioritise data from rating

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4      1      scales (eg Hamilton Rating Scale for Depression) over self-report questionnaires (eg Beck
5
6      2      Depression Inventory).
7
8
9      3      **Risk of bias**
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11     4      Two researchers will independently assess the risk of bias of the included studies using the
12
13     5      Cochrane Collaboration's tool for assessing risk of bias in RCTs (52). For each included RCT,
14
15     6      we will provide a description, comment and judgement of risk of bias for the following
16
17     7      items: (1) bias arising from the randomization process; (2) bias due to deviations from
18
19     8      intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of
20
21     9      the outcome; and (5) bias in selection of the reported result (see Appendix 1 for details).
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23    10      These judgments will be informed by the criteria adapted to the addiction field by the
24
25    11      Cochrane Collaboration. Blinding of participants, personnel and outcome assessor
26
27    12      (avoidance of performance bias and detection bias) will be considered separately for
28
29    13      objective outcomes (e.g. drop out, use of substance of abuse measured by urine analysis,
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31    14      subjects relapsed at the end of follow-up, subjects engaged in further treatments) and
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33    15      subjective outcomes (e.g. duration and severity of signs and symptoms of withdrawal,
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35    16      patient self-reported use of substance, side effects, social functioning as integration at
36
37    17      school or at work, family relationship). Incomplete outcome data (avoidance of attrition
38
39    18      bias) will be considered for all outcomes except for the drop out from the treatment, which
40
41    19      is very often the primary outcome measure in trials on addiction.
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45    20      **Synthesis of data and summary measures**
46
47    21      Data synthesis and meta-analysis
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49    22      For all included RCTs, we will provide a detailed description of the results in both tables and
50
51    23      text. If studies are sufficiently homogeneous to enable meta-analysis, we will pool the data
52

1    for each outcome using a random-effects model in a meta-analysis that compares

2    intervention and control arms, using mean differences or standardized mean differences as

3    appropriate for continuous variables and relative risks for dichotomous outcomes. The

4    meta-analysis will be performed using Review Manager (RevMan V5.3) developed by the

5    Cochrane Community. If meta-analysis is not feasible, we will carry out a narrative summary

6    of studies.

7    In the outcome assessment, for continuous variable outcomes (e.g. quantity of alcohol

8    consumed or scores in depression scales) we will compare standardized mean differences

9    (SMD). For dichotomous outcomes (e.g. participants classified as drinking over set limits or

10    having depression remission), we will compare proportions using risk ratios. Where

11    outcomes have been assessed at more than one time, data for each time point will be

12    extracted. Depending on the availability of sufficient data, we will analyse follow-up

13    durations using different time frames: 1) short term (up to six months post-intervention); 2)

14    medium term (6-12 months post-intervention); and 3) long-term (more than 12 months

15    post-intervention).

16    <u>Unit of analysis issues</u>

17    For trials with more than one - and very similar - control or treatment arms, the results for

18    these arms will be combined in the meta-analysis. If study arms cannot be combined, e.g.

19    due to important differences in intervention characteristics, each pair-wise comparison will

20    be included separately. To avoid the multiple use of participants in the pooled estimate of

21    treatment effect, every arm that is included more than once, will be divided by the number

22    of comparisons where it is included.

1    For dichotomous outcomes, both the total number of patients and the number of events

2    and will be divided up. For continuous outcomes, the means and standard deviations will be

3    left unchanged, and only the total number of participants will be divided. This method

4    retains information from each arm of the trial while it compromises the precision of the

5    pooled estimate slightly.

6    To allow the inclusion of cluster randomised trials with individually randomised trials in the

7    same meta-analysis, we need to account for the relative variability within and between

8    clusters. If a trial report only contains data that is not adjusted for the cluster design, we will

9    add an external estimate of the intra-cluster coefficient (ICC) to estimate a design effect,

10   thus inflating the variance of the effect estimate.

11   <u>Dealing with missing data</u>

12   We will contact authors to try to obtain missing data. Where this is impossible, we will

13   attempt to estimate primary outcome measures using secondary outcome measures; for

14   example, estimating quantity of alcohol consumed using frequency and intensity of

15   consumption. Trials with missing standard deviations will be excluded from the main

16   analysis for the associated continuous measure, but may be included in a sensitivity analysis,

17   using imputed values for the standard deviations.

18   <u>Assessment of heterogeneity</u>

19   Statistical heterogeneity will be assessed for significance with the Cochran's Q test statistic,

20   and quantified with the $I^2$ value (53). Causes of heterogeneity will be explored both

21   narratively and using subgroup and sensitivity analyses.

22   <u>Assessment of publication bias</u>

23   We will evaluate publication bias using the Egger test and funnel plots (54).

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1    <u>Sensitivity analysis</u>

2    We will conduct sensitivity analyses by investigating the effect of restricting to studies with

3    a low overall risk of bias.

4    **Patient and Public Involvement**

5    Patients and the public were not involved in the design and will be not involved in the

6    conduct of the review. However we will discuss the findings with the Newcastle Mental

7    Health Service User Patient and Public Involvement Group and seek their assistance in

8    interpreting the implications for policy and practice.

9    **Timeline**

10    For the complete systematic review and meta-analysis a timeline of nine months is foreseen

11    (1st April 2019 to 31st December 2019).

12    **ETHICS AND DISSEMINATION**

13    As no primary data from studies will be collected, ethical approval is not needed for this

14    systematic review. Findings will be published in peer-reviewed journals and presented at

15    appropriate scientific conferences, congresses and symposia.

16    **CONCLUSION**

17    This review will examine the effectiveness of digital interventions for comorbid excessive

18    drinking and depression. Digital interventions, delivered via computer or mobile phone,

19    have the potential to provide cost-effective support for patients with excessive drinking and

20    depression who may otherwise face socio-economic and structural barriers to treatment.

21    However, whilst previous studies have synthesised evidence of the impact of digital

22    interventions on excessive drinking or depression alone, there is no comprehensive review

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3    1    that considers the effectiveness of such interventions in comorbid populations. This review

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5    2    will respond to this knowledge gap, and thus has the potential to inform the development of

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8    3    evidence-based interventions that could be delivered at scale to this at-risk population.

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11   4    The strengths of this systematic review include the use of an in-depth search strategy and

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13   5    robust quality appraisal criteria to identify and evaluate the existing literature. However

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16   6    potential limitations are likely to include between-study heterogeneity of the original

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18   7    studies and publication bias. Previous research in this field suggests that trials are likely to

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21   8    utilise a range of alcohol consumption and depression measures to assess outcomes (55).

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24   9    Further, whilst we will endeavour to retrieve data from eligible unpublished and non-

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26   10   significant studies, our findings could be limited by publication bias (56).

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29   11   In conclusion, to our knowledge, this study represents the first systematic review of digital

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31   12   interventions for comorbid excessive drinking and depression. Findings will have relevance

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34   13   for healthcare practitioners and policy-makers, as well as helping to inform the direction of

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36   14   future research in this field.

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29  **Patient consent:** Not required.

30  **Word Count:** 2,600 words.

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Appendix 1: Revised Cochrane risk-of-bias tool for randomised trials (RoB 2.0)

## Domain 1: Risk of bias arising from the randomization process

| Signalling questions | Description | Response options |
|---|---|---|
| 1.1 Was the allocation sequence random? | | Y / PY / PN / N / NI |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | | Y / PY / PN / N / NI |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** | | **Low / High / Some concerns** |
| Optional: What is the predicted direction of bias arising from the randomization process? | | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

## Domain 2: Risk of bias due to deviations from the intended interventions

| Signalling questions | Description | Response options |
|---|---|---|
| 2.1. Were participants aware of their assigned intervention during the trial? | | Y / PY / PN / N / NI |
| 2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | Y / PY / PN / N / NI |
| 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | | NA / Y / PY / PN / N / NI |
| 2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups? | | NA / Y / PY / PN / N / NI |
| 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome? | | NA / Y / PY / PN / N / NI |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | | Y / PY / PN / N / NI |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | | NA / Y / PY / PN / N / NI |

| Risk-of-bias judgement | | Low / High / Some concerns |
|---|---|---|
| Optional: What is the predicted direction of bias due to deviations from intended interventions? | | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 2: Risk of bias due to deviations from the intended interventions

| Signalling questions | Description | Response options |
|---|---|---|
| 2.1. Were participants aware of their assigned intervention during the trial? | | Y / PY / <u>PN / N</u> / NI |
| 2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | | Y / PY / <u>PN / N</u> / NI |
| 2.3. <u>If Y/PY/NI to 2.1 or 2.2</u>: Were important co-interventions balanced across intervention groups? | | NA / <u>Y / PY</u> / PN / N / NI |
| 2.4. Could failures in implementing the intervention have affected the outcome? | | Y / PY / <u>PN / N</u> / NI |
| 2.5. Did study participants adhere to the assigned intervention regimen? | | <u>Y / PY</u> / PN / N / NI |
| 2.6. <u>If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4</u>: Was an appropriate analysis used to estimate the effect of adhering to the intervention? | | NA / <u>Y / PY</u> / PN / N / NI |
| Risk-of-bias judgement | | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? | | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 3: Missing outcome data

| Signalling questions | Description | Response options |
|---|---|---|
| 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | | <u>Y / PY</u> / PN / N / NI |
| 3.2 <u>If N/PN/NI to 3.1</u>: Is there evidence that result was not biased by missing outcome data? | | NA / <u>Y / PY</u> / PN / N |
| 3.3 <u>If N/PN to 3.2</u>: Could missingness in the outcome depend on its true value? | | NA / Y / PY / <u>PN / N</u> / NI |
| 3.4 <u>If Y/PY/NI to 3.3</u>: Do the proportions of missing outcome data differ between intervention groups? | | NA / Y / PY / <u>PN / N</u> / NI |

| 3.5 <u>If Y/PY/NI to 3.3</u>: Is it likely that missingness in the outcome depended on its true value? | | NA / Y / PY / <u>PN / N</u> / NI |
|---|---|---|
| **Risk-of-bias judgement** | | **Low / High / Some concerns** |
| Optional: What is the predicted direction of bias due to missing outcome data? | | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

## Domain 4: Risk of bias in measurement of the outcome

| Signalling questions | Description | Response options |
|---|---|---|
| 4.1 Was the method of measuring the outcome inappropriate? | | Y / PY / <u>PN / N</u> / NI |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ? | | Y / PY / <u>PN / N</u> / NI |
| 4.3 <u>If N/PN/NI to 4.1 and 4.2</u>: Were outcome assessors aware of the intervention received by study participants ? | | Y / PY / <u>PN / N</u> / NI |
| 4.4 <u>If Y/PY/NI to 4.3</u>: Could assessment of the outcome have been influenced by knowledge of intervention received? | | NA / Y / PY / <u>PN / N</u> / NI |
| 4.5 <u>If Y/PY/NI to 4.4</u>: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | | NA / Y / PY / <u>PN / N</u> / NI |
| **Risk-of-bias judgement** | | **Low / High / Some concerns** |
| Optional: What is the predicted direction of bias in measurement of the outcome? | | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

## Domain 5: Risk of bias in selection of the reported result

| Signalling questions | Description | Response options |
|---|---|---|
| 5.1 Was the trial analysed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis ? | | <u>Y / PY</u> / PN / N / NI |
| Is the numerical result being assessed likely to have been selected, on the basis of the results, from... | | |

| | | |
|---|---|---|
| 5.2. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | | Y / PY / <u>PN / N</u> / NI |
| 5.3 ... multiple analyses of the data? | | Y / PY / <u>PN / N</u> / NI |
| **Risk-of-bias judgement** | | **Low / High / Some concerns** |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Overall risk of bias

| | | |
|---|---|---|
| **Risk-of-bias judgement** | | **Low / High / Some concerns** |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

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| Section and topic | Item No |
|---|---|
| **ADMINISTRATIVE** | |
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| Authors: | |
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|---|---|
| Meta-bias(es) | 16 |
| Confidence in cumulative evidence | 17 |

| Checklist item |
| --- |

Identify the report as a protocol of a systematic review

If the protocol is for an update of a previous systematic review, identify as such

If registered, provide the name of the registry (such as PROSPERO) and registration number

Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author

Describe contributions of protocol authors and identify the guarantor of the review

If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments

Indicate sources of financial or other support for the review

Provide name for the review funder and/or sponsor

Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol

Describe the rationale for the review in the context of what is already known

Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)

Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review

Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage

Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated

Describe the mechanism(s) that will be used to manage records and data throughout the review

State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)

Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators

List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications

List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale

Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis

Describe criteria under which study data will be quantitatively synthesised

If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's τ)

Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)

If quantitative synthesis is not appropriate, describe the type of summary planned

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Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)

Describe how the strength of the body of evidence will be assessed (such as GRADE)

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**Page Number**

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7  Title, p. 1
8  n/a
9  Prospero Registration number: CRD42019130134, p. 3
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13  p.1
14  p. 19
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17  n/a
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20  Funding sources, p. 19
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p. 13

Studies will be assessed by using various tools and tests. Revised Cochrane risk-of-bias tool for randomised trials (RoB 2.0), p. 10 pp. 21-25; Cochran's Q test statistic (p. 13), PICO (pp. 6-8), Egger test, funnel plots p.13 and by statitical analyses to assess imprecision (effect size estimates) and heterogenity (p.13)

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