An evaluation of the effectiveness of the modalities used to deliver eHealth interventions for Chronic Pain: A systematic review with network meta-analysis

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Abstract:

Background:
eHealth is the use of information and communication technology in the context of healthcare and health research. Recently, there has been a rise in the number of eHealth modalities and the frequency in which they are used to deliver technology-assisted self-management interventions for people living with chronic pain. However, there has been little or no research directly comparing these eHealth modalities.

Objective:
The aim of the current systematic review with a network meta-analysis is to directly compare the effectiveness of eHealth modalities in the context of chronic pain.

Methods:
Randomised controlled trials (N>20 per arm) that investigated technologically delivered interventions for adults with chronic pain were included. Data were extracted on pain severity, psychological distress and HRQoL, and the risk of bias was assessed. Studies were classified by their primary mode of delivery. Pair-wise meta-analyses were undertaken and a network meta-analysis was conducted to generate indirect comparisons of modalities for reducing pain severity.

Results:
The search returned 18,470 studies with 18,349 excluded (duplicates [2,310]; title and abstract [16,039]). Of the remaining papers, 30 studies with 4,595 randomised participants were included in the review. Rankings tentatively indicate that telephone supported interventions are the most effective, with a 46% chance that telephone intervention was the best modality, followed by studies delivered via interactive voice response, internet and virtual reality.

Conclusions:
This current systematic review with a network meta-analysis generated comparisons between previously un-compared technological modalities to determine which delivered the most effective interventions for the reduction of pain severity in chronic pain patients. There are limitations with this review; in particular, the underrepresented nature of some eHealth modalities included in the analysis. However, in the event that the review is regularly updated a clear ranking of eHealth modalities for the reduction of pain severity will emerge.

Keywords: eHealth, Chronic Pain, Systematic Review, Network Meta-Analysis
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PROSPERO: Registration database number: CRD42016035595
eHealth

As technological advances pervade every aspect of daily life, there has been a corresponding proliferation in the development and implementation of technological interventions for health-related purposes. eHealth, the broad term for Information and Communication Technologies deployed in health settings, is a growing area of interest as the international research community attempts to address issues facing modern healthcare [1]. Typically, an eHealth modality is considered to be some specific form of technology that is applied in the context of healthcare [2, 3, 4]. Examples of eHealth modalities include, internet-based [5, 6, 7, 8, 9], telephone supported [10], interactive voice response [11, 12], virtual reality [13, 14], video teleconferencing [15] and mobile phone applications [16, 17].

The core value proposition for delivering healthcare via an eHealth modality is that the barriers experienced by traditional in-person treatment methods are reduced or potentially removed [18, 19, 20, 21, 4]. For instance, an online eHealth intervention may improve accessibility to treatment, reduce the waiting list duration and can be delivered more cost-effectively than in-person services (e.g., [22]). For these reasons, eHealth has gained considerable traction for conditions, which are long term and where there is a shift toward self-management [23, 24, 25, 26]. In this context, where ongoing disease management is required, technology assisted interventions offer a viable and important support option. Many eHealth solutions have been developed for a variety of chronic illnesses, including, diabetes [27, 28], breast cancer [29], hypertension [30], cardiovascular disease [16], multiple sclerosis [31], headache [8] and chronic pain [12, 14, 32, 33, 34, 35, 36, 37, 38].

eHealth and Chronic Pain

Chronic pain refers to pain that lasts for more than three months and persists beyond its biological purpose [39]. Chronic pain is highly prevalent and a leading cause of long-term disability [39]. Much eHealth research has been conducted in the area of chronic pain, and eHealth interventions have shown to be efficacious [40]. However, despite the increasing variety of eHealth modalities used for chronic pain, studies typically focus on one modality and as a result, direct comparisons of modalities are rare [21]. Identifying the need to investigate the relative strengths and weaknesses of modality types, Heapy and colleagues conducted a systematic review of technology-assisted self-management interventions for chronic pain, in which three modality types were evaluated; namely, telephone, interactive voice response and internet. Heapy et al concluded that each modality is effective in the
context of chronic pain, but no conclusive evidence points to one being more superior than the others.

Notably, Heapy and colleagues began the necessary steps toward ascertaining the varying efficacies of each modality as the contributing factor to intervention success, rather simply intervention content. However, the authors recognised certain limitations with their review, such as the breadth of their search strategy (i.e. limited to three databases) and the low number (i.e. three) of included technology types. Moreover, the review included a variety of study designs and while they reported on the between-condition effect sizes when possible, a quantitative comparison (i.e., a meta-analysis) was not conducted. As such, one of Heapy et al.’s indications for future research was to identify the relative efficacy of modality types through direct comparison.

Why is it important to do this review?
While there are a growing number of eHealth interventions for chronic pain, there is a stark lack of research comparing eHealth modalities in this context. Directly comparing eHealth modalities deployed in chronic pain research could potentially yield important insights into which modalities are more efficacious in what context and for what reasons (e.g., treatment fidelity, resource availability, issues with target population, typical engagement levels and cost efficiency). Thus, from the perspectives of patient well-being, healthcare provision and optimising research interventions, there is an impetus to first identify the most effective modalities for chronic pain, and to then investigate why they are the most effective.

The aim of the current study is to add to the literature that concerns itself with evaluating eHealth modalities in the context of chronic pain by directly comparing treatment outcomes across studies that have deployed an eHealth modality. Critically, the current review will conduct a network meta-analysis (NMA) and quantitatively compare and rank the eHealth modalities used for interventions in chronic pain, which has not been done before. A NMA is an extension of a meta-analysis and enables multiple treatments to be compared using direct and indirect comparisons across trials using a common comparator (see [41, 42, 43], for further discussion).

Objective
The objective of the current study is to conduct a systematic review and NMA to evaluate and compare the effectiveness of the eHealth modalities used to deliver interventions (other than drug) for adults living with chronic non-cancer pain.
Outcomes

**Primary Outcomes**: Similar to previous research [44], pain severity was the primary outcome variable. For studies that did not report pain severity, the most relevant pain outcome was extracted (e.g., pain intensity, average pain, or typical pain level experienced).

**Secondary Outcomes**: Secondary outcomes were measures of psychological distress (measures of depression were extracted where available) and health-related quality of life (HRQoL).

Methods

**Protocol and registration**
The systematic review and NMA were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the PRISMA Network Meta-Analysis extension statement (see Appendix 1) [45]. The protocol for this study is registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42016035595) [1].

**Eligibility Criteria**
This study included RCTs that compared eHealth interventions for managing chronic pain with an active eHealth intervention, enhanced control, treatment-as-usual (TAU), and/ or waiting list control; with participants over 18 years who had chronic pain. Studies were full text journal articles published in peer-reviewed journals. The included studies were required to be available in English.

**Classification**
Studies were merged to create nodes representing the primary delivery method (e.g. internet). A study was not included in the network if both arms were classified as the same modality without an additional comparator.

**Information sources**
Four databases; CENTRAL (Cochrane Library), MEDLINE, EMBASE and PsycINFO were searched from inception until 22/11/2017. Necessary changes were made to adapt the search terms for different interfaces. The search strategy is detailed in Appendix 2.

The reference lists of relevant systematic reviews and of included studies were screened to identify any relevant studies. The metaRegister of controlled trials (mRCT) [46],
clinicaltrials.gov [47], and the WHO International Clinical Trials Registry Platform (ICTRP) [48] were also searched.

**Study selection**
Members of the research team screened titles and abstracts to search for duplicate and non-relevant studies, 10% of the papers were assessed in duplicate. Two review authors (SH and KF) independently screened full text papers for inclusion. Studies were included if they: (i) were RCTs; (ii) had N>20 per arm at each time point; (iii) had participants with non-cancer related chronic pain; (iv) were delivered via technological modality; and (v) measured a suitable pain outcome.

**Data collection process and data items**
Data was independently extracted by two authors (BS and SH) into a pre-prepared excel sheet. The following items were extracted: means and standard deviations at post intervention, sample size, measures, mean age, percentage female, diagnosis, mean years of pain, source/method of recruitment and presence of contact with researchers/therapists. If no standard deviations were reported, they were calculated from the available standard errors or confidence intervals.

**Risk of bias**
Risk of bias within individual studies was assessed using the Cochrane Risk of Bias tool. Please see the published protocol for additional detail [1]. Funnel plots and Egger tests were conducted to investigate publication bias across studies.

**Geometry of the Network**
The network includes a node for each technological modality. Additionally, the network contains both a control node (e.g. wait list) and enhanced control node (e.g. education booklet).

**Summary measures**
Standardised mean differences (SMD) between groups at post intervention and measures of uncertainty are reported. Additional summary measures, such as treatment rankings and the probability of each modality arm being the best are reported.

**Planned Methods of Analysis**
**Exploratory analysis**

Random effects pairwise meta-analyses of each available comparison were run as an exploratory analysis using Stata 13 for both primary and secondary outcomes.

**NMA and assessment of inconsistency**

A NMA random effects model of the eHealth modalities, used to deliver chronic pain interventions with the purpose of reducing pain severity, was developed in WinBUGS 14, based on a Bayesian framework, but created with vague priors. The NMA returned pairwise comparisons between all modalities, rankings of the modalities and assessed the probability that each modality is the best. The network contained no closed loop and, thus, no formal test of inconsistency was conducted. Additional information is provided in the protocol [1].

**Additional analyses**

As outlined in the protocol [1], the purpose of adding study level covariates was to reduce heterogeneity by allowing the NMA to take account of additional information and minimising the differences between the studies within each modality. Covariates would be added to the model based on a reduction in the deviance information criterion (DIC). In the present network, the added covariates did not have a significant effect. Sensitivity analyses investigating the influence of priors, initial values, length of burn-in and testing convergence were carried out.

**Results**

**Study selection**

The search returned 18,470 studies (Figure 2). There were 2,310 studies excluded as duplicates and 16,039 studies excluded based on title and abstract. 122 potentially eligible studies were identified and then assessed based on full text. Of these, 92 studies were excluded; 51 were not an RCT, 13 had less than 20 participants per arm at each time point, 7 had patients with cancer related chronic pain, 12 did not deliver the intervention via an eHealth modality, 7 did not measure an appropriate pain outcome and 2 consisted of two arms within the same node without an additional comparator [49, 50]. There were 30 studies included in the analysis.

Figure 1 Flow diagram of studies assessed for eligibility
Study Characteristics

All 30 studies included in this review were two armed RCTs. Each study arm was classified by the primary delivery method (e.g., internet). While the majority of intervention arms were compared with control arms, one study involved the comparison of two active treatments [51]. The 30 studies encompassed 60 arms; 25 internet delivered arms [5, 6, 7, 8, 9, 32, 33, 34, 36, 37, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65], 1 telephone [35], 1 mobile application [51], 2 virtual reality [14, 66], 1 video teleconferencing [15], 1 interactive voice response [12], 18 control and 11 enhanced controls (Table 1).

A total of 4,500 participants were included in the review. There were 2,575 randomised to interventions delivered via a technological modality; internet (n=2,260), telephone (n=124), video teleconferencing (n=65), virtual reality (n=53), mobile applications (n=47), and interactive voice response (n=26).

Table 1 Studies included in the review

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>N*</th>
<th>Measure</th>
<th>Outcome</th>
<th>Attrition**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berman (2009)</td>
<td>Internet (Mind-body) vs Control</td>
<td>78</td>
<td>BPI</td>
<td>Pain Intensity</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>(41, 37)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Boer (2014)</td>
<td>Internet (CBT) vs Enhanced control</td>
<td>43</td>
<td>VAS</td>
<td>Pain Intensity</td>
<td>20.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(20, 23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buhrman (2004)</td>
<td>Internet (CBT) vs control</td>
<td>51</td>
<td>Pain Diary</td>
<td>Pain Intensity</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(22, 29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Treatment Description</td>
<td>n (Arm 1 Arm 2)</td>
<td>Measure</td>
<td>Outcome Description</td>
<td>n</td>
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</tr>
<tr>
<td>Buhrman (2011)</td>
<td>Internet (CBT) vs Control</td>
<td>72 (36, 36)</td>
<td>MPI</td>
<td>Pain Severity</td>
<td>22</td>
</tr>
<tr>
<td>Buhrman (2013a)</td>
<td>Internet (CBT) vs Enhanced control</td>
<td>54 (26, 28)</td>
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<td>Pain Severity</td>
<td>7.4</td>
</tr>
<tr>
<td>Buhrman (2013b)</td>
<td>Internet (ACT) vs Enhanced control</td>
<td>76 (38, 38)</td>
<td>MPI</td>
<td>Pain Severity</td>
<td>22</td>
</tr>
<tr>
<td>Buhrman (2015)</td>
<td>Internet (CBT) vs Enhanced control</td>
<td>52 (28, 24)</td>
<td>MPI</td>
<td>Pain Severity</td>
<td>17.3</td>
</tr>
<tr>
<td>Carpenter (2012)</td>
<td>Internet (CBT) vs Control</td>
<td>131 (63, 68)</td>
<td>PAQ</td>
<td>Pain Average</td>
<td>16.31</td>
</tr>
<tr>
<td>Chiauzzi (2010)</td>
<td>Internet (Self-management) vs Enhanced control</td>
<td>199 (95, 104)</td>
<td>BPI</td>
<td>Pain Intensity</td>
<td>21.1</td>
</tr>
<tr>
<td>Dear (2013)</td>
<td>Internet (CBT) vs Control</td>
<td>62 (31, 31)</td>
<td>BPQ</td>
<td>Pain Average</td>
<td>3.23</td>
</tr>
<tr>
<td>Dear (2015)</td>
<td>Internet (CBT) vs Control</td>
<td>421 (354, 67)</td>
<td>BPQ</td>
<td>Pain Average</td>
<td>10.62</td>
</tr>
<tr>
<td>Dear (2017)</td>
<td>Internet (CBT) vs Enhanced control</td>
<td>164 (76, 88)</td>
<td>WBPQ</td>
<td>Pain Average</td>
<td>7.87</td>
</tr>
<tr>
<td>Garcia-Palacios (2015)</td>
<td>Virtual reality (Activity management) vs Control</td>
<td>61 (31, 30)</td>
<td>BPI</td>
<td>Pain Intensity</td>
<td>3.28</td>
</tr>
<tr>
<td>Henrikssoon (2016)</td>
<td>Internet (Mindfulness) vs Enhanced control</td>
<td>77 (36, 41)</td>
<td>NRS</td>
<td>Pain Intensity</td>
<td>28</td>
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<tr>
<td>Herbert (2017)</td>
<td>Video teleconferencing (ACT) vs Enhanced control</td>
<td>128 (65, 63)</td>
<td>BPI</td>
<td>Pain Severity</td>
<td>41.09</td>
</tr>
<tr>
<td>Krein (2013)</td>
<td>Internet (Pedometer) vs Enhanced control</td>
<td>229 (111, 118)</td>
<td>PI</td>
<td>Pain Intensity</td>
<td>9.6</td>
</tr>
<tr>
<td>Kristjánsdóttir (2013)</td>
<td>Mobile application (CB) vs Internet</td>
<td>87 (47, 40)</td>
<td>VAS</td>
<td>Pain</td>
<td>11.81</td>
</tr>
<tr>
<td>Kroenke (2014)</td>
<td>Telephone (Care management) vs Control</td>
<td>250 (124, 126)</td>
<td>BPI</td>
<td>Pain Intensity</td>
<td>4.8</td>
</tr>
<tr>
<td>Leveille (2009)</td>
<td>Internet (Health Coaching) vs Enhanced control</td>
<td>142 (71, 71)</td>
<td>Pain Site</td>
<td>Pain Average</td>
<td>41.07</td>
</tr>
<tr>
<td>Lin (2017)</td>
<td>Internet (ACT) vs Control</td>
<td>302 (201, 101)</td>
<td>NRS</td>
<td>Pain Intensity</td>
<td>24.17</td>
</tr>
<tr>
<td>Lorig (2008)</td>
<td>Internet (Pain management) vs Control</td>
<td>641 (310, 331)</td>
<td>VNS</td>
<td>Pain</td>
<td>25.03</td>
</tr>
<tr>
<td>Muller (2016)</td>
<td>Internet (Positive Psychology) vs Control</td>
<td>77 (39, 38)</td>
<td>NRS</td>
<td>Pain Intensity</td>
<td>30</td>
</tr>
<tr>
<td>Naylor (2008)</td>
<td>Interactive voice response (CBT) vs Control</td>
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<td>MPQ</td>
<td>Pain Typical</td>
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<tr>
<td>Peters (2017)</td>
<td>Internet (Positive Psychology) vs Control</td>
<td>276 (226, 50)</td>
<td>Pain, this moment</td>
<td>Pain Intensity</td>
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</tr>
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<td>Ruehlman (2012)</td>
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<td>PCP</td>
<td>Pain Severity</td>
<td>7.6</td>
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<td>Strom (2000)</td>
<td>Internet (Applied relaxation) vs Control</td>
<td>45 (20, 25)</td>
<td>Headache Diary</td>
<td>Peak Intensity</td>
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<td>Trompetter (2015)</td>
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<td>Pain Intensity</td>
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<td>Williams (2010)</td>
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<td>Pain Intensity</td>
<td>10.17</td>
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<tr>
<td>Yelvar (2017)</td>
<td>Virtual reality (Physiotherapy) vs Enhanced control</td>
<td>44 (22, 22)</td>
<td>VAS</td>
<td>Pain</td>
<td>4.3</td>
</tr>
</tbody>
</table>

*N displayed as Total N (Arm 1 N, Arm 2 N)
**Displayed as percentage attrition**

**Risk of bias within studies**

Risk of bias summary is presented in Table 2. Seventeen studies were considered to have effectively randomised, twelve did not provide adequate information and one study did not describe randomisation and was judged to be at a high risk of bias. Eleven studies used appropriate methods of allocation concealment, seventeen did not appropriately describe their allocation methods and two studies were judged as high risk given that allocation was not blinded from research assistants. Twenty three studies were not at risk of detection bias; the majority of these administered their assessments online. Seven studies were considered unclear. Thirteen studies provided clear information on their levels of attrition, sixteen were judged to be unclear with many failing to report differences between completers and non-completers, and one study was considered to be at high risk of bias due to statistical differences between the completers and non-completers. Twenty eight studies reported all outcomes and were free from selective reporting bias. Two studies were judged to be of high risk because data could not be extracted. No other sources of bias were found for the 30 studies.

Table 2 Assessment of within study bias

<table>
<thead>
<tr>
<th>Study</th>
<th>Adequate sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>Incomplete outcome data addressed</th>
<th>Free of selective reporting</th>
<th>Free of other bias</th>
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<td>Berman (2009)</td>
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<td>+</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>de Boer (2014)</td>
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<td>+</td>
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</table>
Presentation of network structure

The network map in Figure 2 demonstrates the available evidence for this network. For convenience, the circular nodes are technological modalities and the triangle nodes represent the control groups.

Figure 2 Network map of eHealth modalities for chronic pain

Summary of network geometry

The available evidence was used to generate an anchored indirect treatment comparison network. This type of network has no closed loops and is instead anchored on the internet and control nodes. The number of studies behind each direct comparison is outlined in Table 3, which also includes the percentage contribution that each comparison made to the entire network. As expected, the internet treatment vs control comparison contributes the highest percentage (21.6%) of evidence to the network. Some of the indirect comparisons required a
long pathway to be generated (e.g. comparing mobile applications with telephone treatment requires the direct evidence of the internet and control treatment nodes). The comparisons based on longer paths were communicated with less precision [41].

Table 3 Contribution to the network of direct comparisons

<table>
<thead>
<tr>
<th>Direct Comparison</th>
<th>Number of Studies</th>
<th>Percentage contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virtual reality vs Control</td>
<td>1</td>
<td>9.7%</td>
</tr>
<tr>
<td>Interactive voice response vs Control</td>
<td>1</td>
<td>11.9%</td>
</tr>
<tr>
<td>Internet vs Control</td>
<td>15</td>
<td>21.6%</td>
</tr>
<tr>
<td>Telephone vs Control</td>
<td>1</td>
<td>11.9%</td>
</tr>
<tr>
<td>Virtual reality vs Enhanced control</td>
<td>1</td>
<td>6.6%</td>
</tr>
<tr>
<td>Internet vs Enhanced control</td>
<td>9</td>
<td>15.9%</td>
</tr>
<tr>
<td>Video teleconferencing vs Enhanced control</td>
<td>1</td>
<td>10.6%</td>
</tr>
<tr>
<td>Mobile applications vs Internet</td>
<td>1</td>
<td>11.7%</td>
</tr>
</tbody>
</table>

Results of individual studies

The included studies indicate positive effects for interventions delivered via eHealth modalities in comparison to a control/enhanced control; 20 of 29 studies returned a reduction in pain severity (69%), 20 of 25 studies showed a decrease in psychological distress (80%) and 11 of 14 studies indicated an improvement in HRQOL (79%). Information on effect sizes can be found in the detailed study characteristics tables in Appendix 3.

Synthesis of results

Results of exploratory analysis

Exploratory pairwise meta-analyses were conducted where possible (Table 4).

Table 4 Exploratory Analyses

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>No. of Studies</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internet vs Control</td>
<td>Pain severity</td>
<td>15</td>
<td>0.21 (P&lt;.001)</td>
</tr>
<tr>
<td></td>
<td>Psychological distress</td>
<td>14</td>
<td>0.31 (P=.002)</td>
</tr>
<tr>
<td></td>
<td>HRQOL</td>
<td>5</td>
<td>0.08 (P=.48)</td>
</tr>
<tr>
<td>Internet vs Enhanced control</td>
<td>Pain severity</td>
<td>9</td>
<td>0.18 (P=.31)</td>
</tr>
<tr>
<td></td>
<td>Psychological distress</td>
<td>6</td>
<td>0.19 (P=.07)</td>
</tr>
<tr>
<td></td>
<td>HRQOL</td>
<td>5</td>
<td>0.27 (P=.02)</td>
</tr>
</tbody>
</table>

Pain Severity: A random effects meta-analysis of the comparison returned a pooled SMD of 0.21 (95% CI: [0.12 to 0.31]), suggesting that the participants using internet based interventions had a small but statistically significant difference in pain severity when compared to those on a TAU or wait list control (P<.001). Internet interventions did not result
in a statistically significant difference in pain severity when compared to an enhanced control.

**Psychological Distress:** Of included studies, 25 used a measure of psychological distress. Data were extracted for depression, anxiety, mental health and negative mood regulation using a variety of measures: The Hospital Anxiety and Depression Scale (HADS), Montgomery Asberg Depression Rating Scale (MADRS-Self Rated), Beck Depression Inventory (BDI), Negative Affect Scale (NA), Depression Anxiety Stress Scales (DASS), Patient Health Questionnaire 9-Item (PHQ-9), Personal Health Questionnaire Depression Scale (PHQ-8), SF-8 Health Survey (SF-8), SF-36 and Centre for Epidemiologic Studies Depression Scale (CES-D). Internet delivered interventions returned a statistically significant SMD of 0.31 when compared to a control \( (P = .002) \). Internet delivered interventions did not return a statistically significant reduction in psychological distress when compared to an enhanced control \( (P = .07) \). However, of the six studies included in the meta-analysis, only one did not return a positive effect for the intervention group [60].

**HRQOL:** Data was available on HRQoL for 15 studies. This was measured in a variety of ways including the Quality of Life Interview (QOLI), Patient Global Impression of Change (PGIC), The Quality of Life Index (QLI-Sp), General Health Questionnaire 12-Item (GHQ-12), 12-Item Short Form Survey (SF-12) and the 36-Item Short Form Health Survey (SF-36). No statistically significant differences were found in HRQoL between internet delivered interventions and a control \( (P = .48) \). A small statistically significant increase in HRQoL was found between internet delivered interventions and an enhanced control \( (P = .02) \).

**Results of NMA**
A random effects NMA based on the restricted maximum likelihood estimate was conducted. The generated comparisons (Table 5) indicate that video teleconferencing was significantly worse than all other modalities. The NMA suggests a SMD of 0.2, indicating a small difference between internet and the control, \( (95\% \text{ CrI: } [0.01, 0.39]) \) as expected by the exploratory analysis. Additionally, a SMD of 0.27 was found between internet and the enhanced control \( (95\%: [0.02 to 0.39]) \).

Table 5: Results of random effects NMA
The remaining comparisons had credible intervals containing zero, suggesting a high probability that the true comparison is not significant. Many of the credible intervals were very wide and express the uncertainty in the models estimates. It must be stressed that many of these comparisons were based on a low sample size and do not suggest that significance cannot be achieved with a greater number of studies.

**Modality rankings and probability of being best modality**

Table 6 outlines the rankings of the modalities and the probability that they deliver the most effective interventions. The telephone arm was given the best ranking, at second, but as outlined in the 95% credible interval it could lie anywhere from first to seventh. Slightly less uncertainty surrounds the ranking of the internet arm with a median value of third and a credible interval from first to fifth. Similarly, the ranking of the control arm and the enhanced control display more certainty with a ranking of sixth rated from [5 to 7] and [6 to 7] respectively. The video teleconferencing arm had a ranking of eight with no uncertainty.

### Table 6 Ranked effectiveness of modalities

<table>
<thead>
<tr>
<th>Modality</th>
<th>Rankings*</th>
<th>Probability of being the best**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internet</td>
<td>3 [1 to 5]</td>
<td>.03 (.17)</td>
</tr>
<tr>
<td>Virtual reality</td>
<td>3 [1 to 7]</td>
<td>.16 (.36)</td>
</tr>
<tr>
<td>Telephone</td>
<td>2 [1 to 7]</td>
<td>.46 (.5)</td>
</tr>
<tr>
<td>Mobile applications</td>
<td>5 [1 to 7]</td>
<td>.10 (.30)</td>
</tr>
<tr>
<td>Interactive voice response</td>
<td>3 [1 to 7]</td>
<td>.25 (.44)</td>
</tr>
<tr>
<td>Video teleconferencing</td>
<td>8 [8 to 8]</td>
<td>.00 (.00)</td>
</tr>
</tbody>
</table>

Data displayed as SMD [Credible Interval]
Bolded entries are statistically significant
Table 6 indicates that there is a 46% chance that telephone delivered interventions are the most effective at reducing pain severity. The available evidence suggests that there is a 0% chance that video teleconferencing delivers the most effective interventions.

**Exploration for inconsistency**

As the network contained no closed loops, a formal test of inconsistency could not be conducted, given that the direct and indirect evidence cannot be assessed for conflict. Given that all of the studies included in this review were randomised, the assumption of transitivity is fulfilled.

**Risk of bias across studies**

The funnel plot (see Appendix 4) shows no indication of publication bias with the majority of studies falling within the bands (Egger’s test; $P=.79$). The majority of studies are clustered around the zero line and have relatively large standard errors.

**Results of additional analyses**

Sensitivity analyses were carried out to assess the fit of the model. A variety of different initial values were tested, the model was run with an extended burn in of 200,000. Both a gamma and half normal prior were used to ensure that the normal prior was uninformative and 500,000 and 700,000 iterations were run to ensure that 600,000 were adequate. Additionally the model was run with two chains and history plots showed tight iterations indicating no evidence of non-convergence.

Additional covariates were added to the model to explore heterogeneity. The initial NMA model returned a DIC of 10.65. When the covariates were added to the model the DIC did not significantly reduce and they were considered not to have added enough to the model to warrant inclusion; (age [DIC= 11.31], gender [DIC=11.14], length of intervention [DIC= 10.96], attrition [DIC= 11.27], measure [DIC=10.922], contact [DIC= 10.94], analysis [DIC=11.07], diagnosis [DIC= 11.60]).

**Discussion**
The current study created a ranked list of eHealth modalities used for chronic pain by conducting a systematic review with a network meta-analysis. Study findings tentatively indicate that telephone and interactive voice response are the most effective eHealth modalities for delivering interventions for reducing pain severity. More specifically, the highest ranked modality overall according to NMA analyses was telephone, with a 46% chance that this modality delivered the most effective intervention for reducing pain severity. Following this, interactive voice response had a 25% chance and virtual reality had a 16% chance of being the most effective delivery method. Internet delivered interventions have a 3% chance of being the most effective at reducing pain, however there is more certainty regarding their positioning and effectiveness as they contributed the most papers (24) to the network (comparisons including internet contributed a total of 37.5% to the network). In addition, exploratory analyses revealed that participants who completed internet interventions showed a small reduction in pain severity and decrease in psychological distress compared to those on a wait-list or treatment as usual control (SMD = .21, \( P < .001 \); SMD = .31, \( P = .002 \)).

Exploratory analyses also revealed that psychological distress reduced and HRQoL had a small increase when compared to a wait-list and enhanced control (SMD=.19, \( P = .07 \); SMD=.27, \( P = .02 \)). While the analyses reveal important insights for the potential rank order of eHealth modalities for chronic pain interventions, only tentative conclusions regarding the most effective treatments types can be drawn, as there are limitations with this review.

One limitation is the disproportionate representation of different eHealth modalities included within the network. For example, of the 30 papers included in the analysis, internet was represented in 24, whereas mobile applications, interactive voice response, video teleconferencing and telephone were each represented in only one paper. As a result, while we can be confident of the ranking of internet to the other modalities in the current network, we cannot be confident of the rankings of the other modalities relative to internet. To explain further, if for example, an additional internet paper was added to the current network, the modality rankings would not be anticipated to change; but, if a new study based on another modality was added, then there is a chance the modality rankings would change. However, the review is bound by the available evidence and the current synthesis provides the first steps toward ranking which eHealth methodologies are more efficacious in the context of chronic pain.

It must also be noted that a contributing factor to the limited number of included papers and, therefore eHealth modality types, may have been the restrictive inclusion and exclusion criteria used in the current study. For example, 51 studies were excluded for not
being RCTs and 13 studies were excluded for not having 20 participants per arm for each time point. Therefore, had the eligibility criteria been more relaxed, arguably more studies would have been included allowing for a larger network to be produced. However, the inclusion and exclusion criteria followed on from a previous review in the area and the exacting criteria ensured that the included papers were of high quality and low risk of bias [44].

Finally, due to the heterogeneous nature of intervention content, it may be contentious whether the current approach was optimal to identify the effectiveness of eHealth modalities relative to one another. For example, if each study in the current review administered CBT across each modality type, through accounting for differences in extracted variables (e.g., age and gender), it could be reasonably assumed that any notable differences detected were due to the effect of the modality and not the intervention content (i.e. CBT). However, while this was not the case in the current network, it may also be debated that the aforementioned scenario would actually yield which eHealth modality is best for a particular treatment type (e.g., CBT) and not which eHealth modality is most efficacious in the context of chronic pain. In any case, the scientific and clinical purposes of the current review were to identify which eHealth modality, on the basis of the available evidence, delivers the most efficacious intervention for people living with chronic pain and not which intervention type (e.g., CBT) works best with which eHealth modality.

While there are certain limitations with the current review, the findings provide support for previous research, yield tentative conclusions regarding the ranked efficacy of eHealth modalities in the context of chronic pain and offer insight into further areas for investigation. Similar to previous research [44], the results from the exploratory meta-analysis highlight that internet-delivered interventions can reduce pain severity for people living with chronic pain. Interestingly, with regard to the results from the NMA, the two modalities (telephone and interactive voice response) found, albeit tentatively, to be the most efficacious had some form of human contact during the intervention. Indeed, previous research has shown that therapist contact is important [4], enabling participants to build rapport and maintain engagement. As a result, future research should explore the role of human contact during the eHealth intervention delivery process by conducting, for example, methodological studies within trials varying levels and type of human contact [67, 68]. To yield the true potential of eHealth delivery it would be optimal to identify a substitute or proxy for contact, but in the interim, while this phenomenon is unpacked, eHealth
interventions should consider including some form of human contact during the research process.

As evidenced by the underrepresentation of certain eHealth modalities in this review, more research is required that employs varying eHealth modalities. As noted by Heapy et al, one approach would be to conduct research that directly compares different eHealth modalities [21]. In particular, research should focus on conducting trials with mobile applications for chronic pain. Given the myriad of available mobile applications that exist for people with chronic pain, in their review Bhattarai et al., found 373 for older adults with arthritic pain alone [69], it is concerning that only one study included in the current review delivered an intervention via a mobile application.

In the wider context of eHealth, there are two areas for future work. The first would be to replicate the current synthesis with different chronic conditions. The second area for future work would be to create a core outcome set for eHealth interventions; a standardised set of eHealth intervention engagement outcomes measuring for example fidelity, participant engagement, and user experience. Often, a treatment can have an effect in-person, but this effect may not transfer to an eHealth intervention. In such instances, it is quite possible that the eHealth execution and delivery was unsatisfactory and not that the intervention content cannot be adapted to an eHealth version. A core eHealth outcome set would assist in negating such issues.

In conclusion, from both a clinical and scientific perspective, previous research has outlined a need to compare eHealth modalities in the context of chronic pain. The current research is the first to use a novel statistical method, namely network meta-analysis, to quantitatively compare eHealth modalities in this context. Results suggest that eHealth modalities with human contact (i.e., telephone supported and interactive voice response) are most likely to be effective, but more chronic pain eHealth research is needed. Among many areas for future research, additional research examining underutilised eHealth modalities is recommended and a core outcome set of eHealth interventions in general is paramount.

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**Competing interests**

The authors declare that they have no competing interests.