eHealth interventions for people with chronic kidney disease

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[Intervention Protocol]

eHealth interventions for people with chronic kidney disease

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ABSTRACT

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

This review aims to look at the benefits and harms of using eHealth interventions in the CKD population.

BACKGROUND

Description of the condition

Chronic kidney disease (CKD) is increasingly being recognised as a global public health problem with increasing incidence and prevalence, high costs and poor outcomes (Couser 2011; Levey 2005; Levey 2007). CKD is defined as kidney damage or a measured glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for more than three months or by the presence of albuminuria in two to three spot urine tests (Levey 2005). Poorer patient outcomes and increasing costs are associated with worsening kidney function (Levey 2005).

As CKD progresses it is associated with substantially increased morbidity and mortality. Mortality associated with end-stage kidney disease (ESKD) is 10 to 100 times greater than for age-matched controls with normal kidney function (Couser 2011). Increasing severity of CKD is associated with increased all-cause mortality and cardiovascular disease (CVD) mortality, kidney disease progression requiring life-saving dialysis treatment, acute kidney injury, cognitive decline, anaemia, bone and mineral disorders and bone fractures, and increased hospitalisation and health care usage (Jha 2013; Stevens 2013).

The burden of CKD is rising, as shown by an increase in attributable deaths and the increased incidence and prevalence of ESKD. CKD is especially common in people with other chronic diseases, notably diabetes, hypertension and cardiovascular disease, and multiplies the risk for adverse outcomes and increases costs (Couser 2011; Levey 2007). The prevalence of CKD is estimated to affect 8% to 16% of people worldwide (Jha 2013), with the annual growth of ESKD treatments ranging from 6% to 12% over the past two decades (Couser 2011).

It has been estimated that developed countries spend approximately 2% to 3% of their annual health care budget on ESKD,

with earlier stages of CKD costing approximately double this (Couser 2011; Jha 2013). The economic burden of CKD has not been well evaluated in developing countries but it is expected to be higher than in developed countries (Jha 2012).

Description of the intervention

Patient engagement and self-management are the cornerstones of optimal chronic disease management. Current literature regarding patient self-management, education and engagement in the CKD population is lacking. Literature indicates an improvement in patient knowledge, improvement in health-related quality of life, delayed need for dialysis, improved clinical outcomes, improved adherence to therapeutic treatments and medications and increased survival when utilising self-management programs (Bonner 2014; Chen 2011; Devins 2005). It has also been noted that interventions incorporating cognitive or behavioural components regarding adherence to diet, fluid, medication and dialysis treatment are more effective in the haemodialysis population (Matteson 2010). However, there are few randomised controlled trials (RCT) and within these there are significant variations in length of interventions, study designs, outcomes assessed and measurement of outcomes (Bonner 2014; Matteson 2010).

With CKD and renal replacement therapy rising, it is essential to find innovative and efficient ways to engage with this patient population and improve health behaviours and outcomes. Delivering patient-centred care and optimising self-management is a priority, to control risk factors and improving disease management (Tong 2007). Modifiable CKD risk factors such as weight, blood glucose control, blood pressure (BP) control and poor dietary intake are associated with increasing morbidity and mortality (Couser 2011). The World Health Organization has recommended that interventions focus on effective methods, including cost effective methods, to control modifiable risk factors such as lifestyle interventions, reducing hypertension, improving glycaemic control and cardiovascular risk factors (e.g. dyslipidaemia) (Couser 2011). Electronic health (eHealth) has been defined as an "emerging field in the intersection of medical informatics, public health and business, referring to health services and information delivered or enhanced through the Internet and related technologies…the term characterizes not only a technical development, but also a state-of-mind, a way of thinking, an attitude, and a commitment for networked, global thinking, to improve health care locally, regionally, and worldwide by using information and communication technology" (Eysenbach 2001). eHealth interventions encompass internet-based systems, telemedicine, mobile phone technologies (e.g. text messaging, mobile phone applications), consumer health informatics, and healthcare information systems using computer-based technologies.

Worldwide there has been a tremendous increase in the use of technologies. The use of the Internet in America has increased from 52% in 2000 to 84% in 2015, and currently it is estimated that 89% of Americans own a mobile phone, with 64% owning a smart phone (Perrin 2015; Smith 2015). Whilst rates of Internet and phone use are lower in developing countries there is a similar trend. It is currently estimated that 86% of people own a mobile phone, 66% use the Internet, and 38% own a computer (Pew Research Center 2015). Use of technology is associated with younger age, higher education attainment and higher socio-economic groups (Perrin 2015; Smith 2015). In the chronic disease population it has been estimated that 62% use the Internet and 51% use the Internet to look for medical information (Fox 2010). There is currently no published data regarding the use of technology in the CKD population.

There is a variety of different eHealth modalities reported in the literature, including:

- Telehealth technologies
- Mobile phone based (including text messaging and the use of applications on mobile phones)
- Internet and computer based
- Mixed methods (incorporating telehealth, Internet and mobile phone technologies)

Within these eHealth interventions there is wide use of these tools, which can be categorised in two ways:

- Patient self-management interventions
- Clinician decision support tools

These varying eHealth interventions are also employed in various ways:

- eHealth in addition to usual care
- eHealth as a stand-alone intervention

Recently there has been an increase in availability of eHealth interventions aiming to improve chronic disease management and patient outcomes. With the bourgeoning use of technologies in all facets of people's lives, technology provides a new opportunity to engage with people to improve health behaviours. eHealth offers the opportunity to reach those populations who are most at risk of reduced access to healthcare and worse health outcomes (e.g. remote communities, lower socio-economic groups, developing countries) with high uptake of technology in these populations. With more people using technology, the development, adoption and implementation of eHealth holds tremendous promise to improve consumer access to relevant health information, enhance the quality of care and encourage the adoption of healthy behaviours.

How the intervention might work

In the CKD population, achieving some understanding of the disease condition is an important component of promoting self-management and shared decision making that can contribute to improved medication compliance (e.g. medications relating to BP, renal bone disease and proteinuria), avoiding potentially nephrotoxic substances (e.g. non-steroidal anti-inflammatory medica-

tions), attending appointments and improving health-related behaviours (e.g. diet, exercise and smoking cessation) (Fraser 2013). The prevention of CKD, and delaying its progression to ESKD, requires complex care because it involves both specific CKD management, as well as management of other prevalent co-morbidities (Lopez-Vargas 2014). Therefore, employing novel strategies to improve the current management of this disease is vital.

Currently, there is limited literature regarding the use of eHealth technologies in the CKD population. A review exploring the effectiveness of telehealth in kidney care (studies included pre-dialysis, dialysis-dependent and post kidney transplant patients) found that this was a variable alternative to face-to-face care in terms of clinical outcomes and patient satisfaction (Blinkhorn 2012).However, there was only a small number of studies, only one of which was a RCT. The author highlighted the lack of available literature in the CKD population compared to other chronic disease conditions. However, as review did not include studies involving other technological interventions such as computer or mobile phone technologies, further review of the literature in CKD is warranted.

Clinical outcomes

eHealth interventions have shown mixed results in a range of clinical outcomes when compared to usual care or non eHealth interventions.

Cardiovascular disease

A review by Widmer 2015 reported significant improvements in a number of CVD clinical outcomes with the use of digital health interventions over a six to 12 month period in a mixed CVD population (primary care, secondary care and heart failure). In those studies which contained analysable CVD outcome data, a significant 40% relative risk reduction in CVD outcomes (e.g. myocardial infarction, stroke, revascularisation, hospitalisation) and all-cause mortality and a significant 1.25% reduction in the Framingham 10 year risk percentages was reported. However, as only a small subset of studies contained analysable data and as such this effect size should be interpreted with caution. It was reported that there was also a significant reduction in CVD risk factors, weight, body mass index, cholesterol levels and BP, in secondary and heart failure populations. The most efficacious interventions were web, text messaging or telemedicine, with no effect reported with email-based interventions.

Diabetes

In a review by Zhai 2014 a significant improvement in glycaemic control, measured using HbA1c, when analysing all telemedicine modalities. Pooled analyses showed significant improvement in glycaemic control with both internet-based and phone-based interventions (in addition to usual care). However, there was no change in glycaemic control when analysing interventions using internet transmission (e.g. patients uploading blood results using the Internet, telephone or Bluetooth).

A meta-analysis conducted by Pal 2013 showed a small but significant improvement in HbA1c of 0.2% of all eHealth interventions compared to control; this improvement was more pronounced in mobile phone based interventions with a 0.5% reduction in HbA1c. It was noted that in interventions measuring outcomes greater than six months there were no statistical significant changes in glycaemic control, suggesting that the effects of these interventions may wear off (Pal 2013).

Cotter 2014 reported no significant change when using various eHealth interventions in HbA1c levels in a type 2 diabetic population. Those studies that did show improvements included interactive components with tracking and personalized feedback, and provided opportunities for peer support.

Smoking cessation

A number of eHealth technologies, particularly mobile phone interventions have shown promising results. It has been reported that the use of intensive, personalised mobile phone interventions, in the form of text messages, (Free 2011; Rogers 2005; Whitaker 2016) have greater impact in smoking cessation for six weeks or longer, when compared to usual care or passive interventions. Intensive, personalised text messaging interventions have been shown to double quit rates at six weeks (Rogers 2005) and six months (Free 2011) when compared to usual care. These positive results were also reflected in a meta-analysis conducted by Whitaker 2016 which showed a significant 71% increase in long-term quit rates when comparing personalised, intensive text message interventions when compared to usual care. However a systematic review conducted by Civljak 2013 failed to show any significant improvements in smoking cessation with the use of interactive, tailored internet-based interventions. There was some evidence that interactive Internet-based interventions were more effective at improving long-term quit rates than usual care (e.g. printed self-help books), however this was not significant. There was no difference found between interactive, tailored internet-based interventions versus interactive non-internet-based interventions (e.g. phone and face-to-face counselling) and passive internet-based interventions.

Weight loss

Approximately 50% of technology-based weight loss studies reported a significant reduction in weight compared to controls in a systematic review conducted by Raajimakers 2015. Five key components that enhanced technology-based interventions included: self-monitoring, counsellor feedback and communication, group support, the use of a structured program and the use of individually tailored programs. It was reported that interventions incorporating four to five of these components showed significantly

greater weight loss when compared to usual care, while those studies incorporating only one to three of these strategies had mixed results (Raajimakers 2015).

Mixed outcome measures

Murray 2005 and Hamine 2015 conducted systematic reviews in mixed chronic disease populations using internet-based and mobile phone based interventions (known as mHealth), respectively. Murray 2005 reported no change in a range of clinical outcomes, including urinary incontinence, weight and HbA1c with the use of internet-based interventions that incorporated at least one component of social support, decision support, or behaviour change support. Less than half (39%) of studies reported significant improvements in clinical outcomes with the use of mHealth interventions. Clinical outcome measures were reported in diabetes (HbA1c, frequency of hypoglycaemic events, and changes in insulin dosage), CVD (changes in BP, lipid profile and CVD risk profile) and chronic lung disease (indicators of lung function, use of nebulizers, and exercise tests) (Hamine 2015).

A systematic review conducted by Beratarrechea 2014 investigated the use of mobile phone interventions used in chronic disease in developing countries reported positive results. Significant improvements in pulmonary function were reported in Taiwan and Croatia with the use of a text message intervention. Similarly, text message interventions in Poland and India showed significant improvements in glycaemic control, measured using HbA1c. While a study conducted in Uruguay showed no significant improvement in HbA1c when utilising an internet-based plus text message intervention, it was noted that uptake of this intervention was very poor, particularly with respect to the internet-based component. This review indicates that mobile health interventions are emerging as a useful to improve clinical endpoints in developing countries, however there are limited studies and the authors recommend future research is needed.

Patient-centred outcomes

Patient-centred outcomes are related to "survival, function, symptoms, and health-related quality of life". It "incorporates a wide variety of settings and diversity of participants to address individual differences and barriers to implementation and dissemination and investigates optimizing outcomes while addressing burden to individuals, resource availability, and other stakeholder perspectives" (Patient Centred Outcomes Research 2013).

Patient engagement

eHealth interventions have shown promise in improving patient engagement. In a systematic review exploring various eHealth interventions including, Internet, mobile phone, telehealth and health information management tools, showed an improvement in patient engagement and improvement in clinical outcomes (Barello 2015). However, similarly to face-to-face interventions, quality of the patients' experience should be paramount when designing these interventions, with the need to undertake a holistic view of the patient and to be able to directly engage with the patient about their healthcare (Barello 2015). This was also highlighted in a review of the efficacy of online patient portals which found that early patient engagement in the development of these programs regarding health literacy and usability led to better uptake and engagement of the intervention (Irizarry 2015). Additionally, providing personalised, tailored information was more effective (Irizarry 2015). There is a paucity of available research and significant heterogeneity in the eHealth landscape and this hinders any assertion regarding the most efficacious interventions to enhance patients' self-management. Barriers to eHealth include access to technology, technology literacy and technical issues (Barello 2015; Irizarry 2015).

Adherence

Improvement in adherence and attendance rates was mixed (Beratarrechea 2014; Hamine 2015). Beratarrechea 2014 reported improved clinic attendance in the majority of studies which used text message reminders. Tailored text message interventions were found to significantly improve medication adherence in diabetic, CVD and chronic lung disease populations, however increased adherence was reported in only 56% of mobile phone-based studies (Hamine 2015).

Health-related quality of life and social support

Two reviews reported on social support and health related quality of life (Murray 2005; Pal 2013). In Pal 2013 the use of interactive computer based interventions in a diabetic population showed either small improvements or no change in mood, health related quality of life or physical activity. In a mixed chronic disease population, including both adults and children, computer and internet-based interventions had a significantly positive effect on social support and a likely positive impact on self-efficacy (Murray 2005). Murray 2005 also reported non-significant positive impacts on behavioural outcomes such as physical activity, dietary intake and attendance.

Diet and physical activity

A systematic review by Cotter 2014 investigating the effectiveness of internet-based interventions in type 2 diabetes showed no significant changes in dietary behaviours or physical activity levels. These internet-based applications provided a variety of mechanisms to promote behaviour modification, ranging from static education, to structural goal setting and progress tracking tools to platforms for social support. The authors noted that similarly to non-internet-based interventions, achieving adherence to healthy

behaviours over time is one of the biggest challenges for any internet-based behavioural intervention. They also noted that Internet utilisation reduces over time; however there is not enough evidence to suggest optimal patterns or length of use with the current research.

Usability and acceptability

There is limited reported data regarding usability, feasibility and acceptability. In a review by Hamine 2015 it was reported that overall usability, feasibility and acceptability were high among end-users and that these interventions contributed to increased self-management awareness and knowledge about the chronic disease. It was also highlighted that there was good comprehension and satisfaction across diverse populations (low income, bilingual populations and difficult to reach populations) and features such as automated reminders, text messages with education and motivational content, healthy living challenges and wireless transmission of data contributed to increased reported self-management awareness and knowledge about disease management (Hamine 2015).

Cost effectiveness

Data regarding the cost-effectiveness of eHealth interventions was limited. Beratarrechea 2014 reported reduced costs associated with employing a text message appointment reminder system and it was estimated that text message interventions cost 35% to 45% less than telephone-based reminder systems. Zhai 2014 and Murray 2005 reported it was not possible to draw conclusions regarding the cost effectiveness of the eHealth interventions due to limited data.

eHealth interventions are becoming seen as a viable option to promote behaviour change, disease management and improve clinical outcomes in many different for chronic disease conditions. There are promising outcomes of using eHealth interventions, when used in additional to traditional counselling techniques, for improving disease management in chronic disease populations. However there is a paucity of well-designed studies and further research is needed to ascertain the optimal type, intensity and duration of eHealth strategies to most effectively elicit knowledge and behaviour change. However, given the current literature showing positive trends for the use of eHealth in chronic disease management and health behaviour change, it is foreseeable that the CKD population could also benefit from the use of eHealth interventions.

Why it is important to do this review

This review is important for a number of reasons:

1. With CKD rising, effective strategies for improving patient outcomes, improving the effectiveness of our interventions and reducing costs is vital to reduce morbidity and mortality associated with all stages of CKD worldwide.

2. eHealth interventions are becoming more common and people are becoming more reliant on technology across all age groups. There is a revolution in the modern health care system powered by the growth of different health information technologies that hold tremendous promise for enhancing the delivery of health care (Kreps 2010). Whilst there has been a large increase in the number studies investigating eHealth interventions due to significant heterogeneity, with respect to methods and chronic disease groups, it is unclear what the most efficacious interventions are. It is vital to determine which eHealth strategies are effective in improving CKD management and patient outcomes.

OBJECTIVES

This review aims to look at the benefits and harms of using eHealth interventions in the CKD population.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alteration, use of alternate medical records, date of birth or other predictable methods) will be included.

Types of participants

Adults and children who have been diagnosed with CKD will be included in this study.

Diagnosis of CKD is defined by estimated GFR (eGFR) less than 60mL/min or, eGFR less than 90 mL/min with albuminuria or haematuria, for at least 3 months or as defined using other clinically indicated criteria.

Types of interventions

Any interventions that the authors report to be using eHealth technologies to promote behaviour change in CKD. eHealth technologies include:

- Telephone and Telehealth
- Mobile phone (including applications available on these devices)

- Computers and tablets (including applications available on these devices)
- Personal Digital Assistants
- Internet (including e-mail)
- Electronic transmission (e.g. using technologies such as Bluetooth)
- Social Media
- Electronic decision support tools

The comparisons will be as follows.

1. eHealth intervention versus non-eHealth intervention
2. eHealth intervention versus alternate eHealth intervention
3. eHealth intervention versus no intervention or usual care

If meta-analysis are possible, technologies of the same classifications (e.g. online or web) will be grouped together for analysis. If possible, meta-regression analysis will be used to determine what elements of the eHealth interventions were most effective.

Types of outcome measures

Time intervals at which outcome assessment takes place may affect the effect of the intervention programs. We will consider all time frames used by authors.

1. Changes in clinical parameters
    - Change electrolyte management (measured using biochemical measurements)
    - Change in kidney function (measured using eGFR and/or serum creatinine)
    - Change in fluid management (measured using inter-dialytic weight gains)
    - Change in co-morbidities (measured using BP control, dyslipidaemia, HbA1c, fasting and random blood glucose readings, anthropometry)
    - Hospitalisation rates
    - Mortality
2. Changes in patient parameters
    - Dietary intake and behaviours (measured using self-reported data and qualitative and quantitative surveys)
    - Physical activity behaviours (using validated tools, quantitative and qualitative surveys, self-reported data)
    - Adherence to treatment, including appointments (using validated or self-reported data)
1. - Quality of life (measured using validated tools such as the SF-36 which exploring vitality, physical functioning, pain, health perception, mental health and social, physical and emotion role function)
    - Nutritional status (measured using validated tools)
    - Changes in self-management and self-efficacy
    - satisfaction with interventions
2. Cost effectiveness
    - Incremental cost-effectiveness ratios (defined as the cost per quality-adjusted life year gained)
    - Cost per Disability Adjusted Life Years (DALY)
    - Costs associated with eHealth intervention

4. Potential harms
    - Additional patient or health professional time associated with the use of eHealth intervention
    - Accidents or accidental deaths associated with using the eHealth intervention (e.g. reading text message while driving)

Search methods for identification of studies

Electronic searches

We will search the Cochrane Kidney and Transplant Specialised Register through contact with the Information Specialist using search terms relevant to this review. The Specialised Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of clinical practice guidelines, review articles and relevant studies
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.
3. Published governmental reports and white papers

Data collection and analysis

Selection of studies

The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts will be screened independently by two authors who

will discard studies that are not applicable. However, studies and reviews that might include relevant data or information on studies will be retained initially. Two authors will independently assess retrieved abstracts, and if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria.

Data extraction and management

Data extraction will be carried out independently by the same authors using standard data extraction forms. Studies reported in non-English language will be translated before assessment. Where more than one publication of a study exists, only the publication with the most complete data will be included. Where relevant outcomes are only published in earlier versions these data will be used. Any discrepancy between published versions will be highlighted. Any further information required from the original author will be requested by written correspondence and any relevant information obtained in this manner will be included in the review. Disagreements will be resolved in consultation a third author.

Assessment of risk of bias in included studies

The following items will be independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
    - Participants and personnel (performance bias)
    - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (e.g. incidence of ESKD, mortality) results will be expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (e.g. quality of life, body weight), the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used.

Unit of analysis issues

Cluster RCTS will be analysed in one of two ways.

1. Using a statistical analysis that properly accounts for the cluster design. Some examples of these are based on a 'multi-level model', a 'variance components analysis' or may use 'generalised estimating equations' (Higgins 2011).
2. Conduct the analysis treating the sample size as the number of clusters and proceed as if the study was individually randomised, treating the clusters as individuals.

When considering cross-over studies we will only use data from the first period.

When considering studies with multiple treatment groups we will try to combine all relevant experimental intervention groups of the study into a single group and to combine all relevant control intervention groups into a single group to enable single pair wise comparison.

Dealing with missing data

Any further information required from the original author will be requested by written correspondence (e.g. emailing corresponding author) and any relevant information obtained in this manner will be included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population will be carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals will be investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) will be critically appraised (Higgins 2011).

Assessment of heterogeneity

We will first assess the heterogeneity by visual inspection of the forest plot. Heterogeneity will then be analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). A guide to the interpretation of I^2 values will be as follows.

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

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a confidence interval for I^2) (Higgins 2011).

Assessment of reporting biases

If possible, funnel plots will be used to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

Data will be pooled using the random-effects model but the fixed-effect model will also be used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be used to explore possible sources of heterogeneity (e.g. participants, interventions and study quality). Heterogeneity among participants could be related to age, stage of CKD or underlying concurrent disease states (e.g. diabetes). Heterogeneity in eHealth interventions could be related to the way the intervention is delivered (e.g. one on one, internet-based, or in groups), the content of the intervention (e.g. lifestyle interventions or medication compliance interventions) or the duration of the intervention.

If a meta-analysis is not possible, adverse effects will be tabulated and assessed with descriptive techniques, as they are likely to be different for the various interventions used. Where possible, the risk difference with 95% CI will be calculated for each adverse effect, either compared to no treatment or to another intervention.

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of the following factors on effect size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, as specified
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

'Summary of findings' tables

We will present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We plan to present the following outcomes in the 'Summary of findings' tables.

The seven key outcomes to be included in the Summary of Findings table are as follows.

- Change electrolyte management
- Change in fluid management
- Dietary intake and behaviours
- Physical activity behaviours
- Adherence to treatment
- Quality of life.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Kidney Diseases] explode all trees 2. MeSH descriptor: [Renal Replacement Therapy] explode all trees 3. MeSH descriptor: [Renal Insufficiency] explode all trees 4. MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees 5. dialysis:ti,ab,kw (Word variations have been searched) 6. hemodialysis or haemodialysis:ti,ab,kw (Word variations have been searched) 7. hemofiltration or haemofiltration:ti,ab,kw (Word variations have been searched) 8. hemodiafiltration or haemodiafiltration:ti,ab,kw (Word variations have been searched) 9. kidney disease* or renal disease* or kidney failure or renal failure:ti,ab,kw (Word variations have been searched) 10. ESRF or ESKF or ESRD or ESKD:ti,ab,kw (Word variations have been searched) 11. CKF or CKD or CRF or CRD:ti,ab,kw (Word variations have been searched) 12. CAPD or CCPD or APD:ti,ab,kw (Word variations have been searched) 13. predialysis or pre-dialysis:ti,ab,kw (Word variations have been searched) 14. {or #1-#13} 15. (sms or mms) and messag*:ti,ab,kw (Word variations have been searched) 16. apps:ti,ab,kw (Word variations have been searched) 17. text messag*:ti,ab,kw (Word variations have been searched) 18. multimedia messag*:ti,ab,kw (Word variations have been searched) 19. facebook*:ti,ab,kw (Word variations have been searched) 20. email*:ti,ab,kw (Word variations have been searched) 21. twitter* or tweet*:ti,ab,kw (Word variations have been searched) 22. social media*:ti,ab,kw (Word variations have been searched) 23. (mobile* or cell or smart*) and phone*:ti,ab,kw (Word variations have been searched) 24. ios or android:ti,ab,kw (Word variations have been searched) 25. ipad* or iphone* or ipod*:ti,ab,kw (Word variations have been searched) 26. tablet* and computer*:ti,ab,kw (Word variations have been searched) 27. (online or web*) and (education* or train*):ti,ab,kw (Word variations have been searched) 28. personal digital assistant*:ti,ab,kw (Word variations have been searched) 29. e-health or ehealth or mhealth or m-health or telehealth or telemedicine:ti,ab,kw (Word variations have been searched) 30. {or #15-#29} 31. {and #14, #30}
MEDLINE	1. exp Telemedicine/ 2. exp Internet/ 3. exp communications media/ 4. exp Programmed Instruction as Topic/ 5. Computers, Handheld/ 6. Mobile Applications/ 7. exp Cell Phones/ 8. ((sms or mms) and messag$).tw. 9. apps.tw. 10. "text messag$".tw.

(*Continued*)

	11. multimedia messag$.tw. 12. facebook.tw. 13. email$.tw. 14. (twitter or tweet$).tw. 15. social media$.tw. 16. ((mobile$ or cell or smart$) and phone).tw. 17. (ios or android$).tw. 18. (ipad$ or iphone$ or ipod$).tw. 19. (tablet$ and computer$).tw. 20. ((online or web$) and (education$ or train$)).tw. 21. personal digital assistant$.tw. 22. (e-health or ehealth or mhealth or m-health or telehealth$ or telemedicine$).tw. 23. or/1-22 24. Kidney Diseases/ 25. exp Renal Replacement Therapy/ 26. Renal Insufficiency/ 27. exp Renal Insufficiency, Chronic/ 28. dialysis.tw. 29. (hemodialysis or haemodialysis).tw. 30. (hemofiltration or haemofiltration).tw. 31. (hemodiafiltration or haemodiafiltration).tw. 32. (kidney disease* or renal disease* or kidney failure or renal failure).tw. 33. (ESRF or ESKF or ESRD or ESKD).tw. 34. (CKF or CKD or CRF or CRD).tw. 35. (CAPD or CCPD or APD).tw. 36. (predialysis or pre-dialysis).tw. 37. or/24-36 38. and/23,37
EMBASE	1. exp telehealth/ 2. exp mass communication/ 3. exp mobile application/ 4. ((sms or mms) and messag$).tw. 5. apps.tw. 6. “text messag$”.tw. 7. multimedia messag$.tw. 8. facebook.tw. 9. email$.tw. 10. (twitter or tweet$).tw. 11. social media$.tw. 12. ((mobile$ or cell or smart$) and phone).tw. 13. (ios or android$).tw. 14. (ipad$ or iphone$ or ipod$).tw. 15. (tablet$ and computer$).tw. 16. ((online or web$) and (education$ or train$)).tw. 17. personal digital assistant$.tw. 18. (e-health or ehealth or mhealth or m-health or telehealth$ or telemedicine$).tw. 19. or/1-18 20. exp renal replacement therapy/

(*Continued*)

	21. kidney disease/ 22. chronic kidney disease/ 23. kidney failure/ 24. chronic kidney failure/ 25. mild renal impairment/ 26. stage 1 kidney disease/ 27. moderate renal impairment/ 28. severe renal impairment/ 29. end stage renal disease/ 30. renal replacement therapy-dependent renal disease/ 31. kidney transplantation/ 32. (hemodialysis or haemodialysis).tw. 33. (hemofiltration or haemofiltration).tw. 34. (hemodiafiltration or haemodiafiltration).tw. 35. dialysis.tw. 36. (CAPD or CCPD or APD).tw. 37. (kidney disease* or renal disease* or kidney failure or renal failure).tw. 38. (CKF or CKD or CRF or CRD).tw. 39. (ESRF or ESKF or ESRD or ESKD).tw. 40. (predialysis or pre-dialysis).tw. 41. ((kidney or renal) adj (transplant* or graft* or allograft*)).tw. 42. or/20-41 43. and/19,42

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random)
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central

(*Continued*)

	allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed

(*Continued*)

	event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline

(*Continued*)

	imbalance; has been claimed to have been fraudulent; had some other problem
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: JS, JC, AW, KC, VL, CC
2. Study selection: JS, ZC
3. Extract data from studies: JS, ZC
4. Enter data into RevMan: JS, ZC
5. Carry out the analysis: JS, ZC
6. Interpret the analysis: JS, ZC
7. Draft the final review: JS, JC, AW, KC, VL, CC
8. Disagreement resolution: VL
9. Update the review: JS

DECLARATIONS OF INTEREST

None known

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