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[Intervention Review]

Computer and mobile technology interventions to promote medication adherence and disease management in people with thalassemia

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ABSTRACT

Background

Thalassemia syndromes are inherited hemoglobin disorders that result when the synthesis of normal hemoglobin is lacking or significantly reduced. For people with thalassemia, long-term red blood cell transfusion remains the mainstay of therapy, which may lead to iron overload causing severe complications and damage in different body organs. Long-term iron chelation therapy is essential for people with thalassemia to minimize the ongoing iron-loading process. In addition, suboptimal adherence can increase adverse events associated with iron overload and result in increased morbidity, mortality, healthcare utilization and cost of care.

Objectives

To identify and assess the effects of computer and mobile technology interventions designed to facilitate medication adherence and disease management in individuals with thalassemia, including:

- evaluating the effects of using computer and mobile technology interventions for medication adherence and disease management on health and behavioral outcomes;
- identifying and assessing the effects of computer and mobile technology interventions specific to different age groups (children, adolescents and adults) and type of modality (e.g. cell phone, the Internet).

Search methods

We searched CENTRAL (the Cochrane Library), MEDLINE, Embase, CINAHL, PsycINFO, ProQuest Dissertations & Theses Global, Psychology and Behavioral Sciences Collection, Web of Science Science & Social Sciences Conference Proceedings Indexes, IEEE Xplore and ongoing trial databases (22 February 2018). We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register (20 June 2019). We also searched for unpublished work in the abstract book of nine major conferences in the related field.

Selection criteria

Randomized controlled trials (RCT) and quasi-RCTs comparing single- or multi-component interventions versus no intervention, placebo or standard care, with adherence to iron chelation as the primary outcome were eligible for inclusion. Non-randomized studies of interventions, controlled before-after studies, and interrupted-time-series studies were also eligible for inclusion.

Data collection and analysis

Three authors independently assessed study eligibility. If we had included any studies, we would have independently assessed risk of bias and extracted data; we planned to assess the quality of the evidence using GRADE.

Main results

We did not identify any eligible studies for inclusion in the review.

Authors' conclusions

Due to lack of evidence, we cannot comment on the efficacy or effectiveness of computer and mobile technology intervention strategies to promote disease management and adherence to iron chelation therapy in people with thalassemia.

We concluded that RCTs are needed to examine a variety of computer and mobile technology intervention strategies that may be useful for promoting disease management and increasing adherence to iron chelation therapy in individuals with thalassemia.

PLAIN LANGUAGE SUMMARY

Strategies to improve disease management and increase adherence to iron chelation therapy in people with thalassaemia

Review question

We wanted to see if there were any interventions using computer and mobile technology (e.g. cell phone, the Internet) that would help people manage their thalassemia better and adhere more to their iron chelation therapy.

Background

People with thalassaemia, who receive regular transfusions, are exposed to excess iron in their body. This can result in medical complications, including organ damage and death. Some medications are used to remove excess iron in the body, but these treatment schedules can be difficult to follow and have undesirable side effects.

Search date

The evidence is current to 20 June 2019.

Study characteristics

We searched the literature for both randomized and non-randomized studies, and found none which were eligible for inclusion.

Key results

We found no eligible studies of computer and mobile technology intervention strategies for individuals with thalassemia.

Quality of evidence

We did not identify any evidence for inclusion in the review.

BACKGROUND

Description of the condition

Thalassemia syndromes are inherited hemoglobin disorders that result when the synthesis of normal hemoglobin is lacking or significantly reduced (Martin 2013). Approximately 5% of the world's populations are estimated to carry one variant globin allele with over 300,000 newborns affected with the disease (i.e. thalassemia syndrome) every year (Weatherall 2012).

Thalassemia syndromes include either alpha (α) thalassemia or beta (β) thalassemia. α -thalassemia is caused by either absent or decreased production of α -globin chains and its clinical severity varies based on the number of alleles affected as well as the type of genetic mutation (Higgs 2010). β -thalassemia is caused by either absent or decreased production of β -globin chains and its clinical presentation can be as early as the first six months of life with moderate to severe anemia, or in early childhood with symptoms such as anemia, jaundice, abdominal distention, hepatosplenomegaly and poor growth (Rund 2005). People with transfusion-dependent thalassemia (TDT) require blood transfusions on a regular basis, on average 8 to 12 times or more per year. In contrast, those with non-transfusion-dependent thalassemia (NTDT) can maintain an adequate hemoglobin level and require packed red blood cell (RBC) transfusions only in times of physiologic stress, or fewer than eight times per year (Martin 2013; Rund 2005). For people with thalassemia, stem cell transplantation is the only curative treatment option (Angelucci 2010) and long-term RBC transfusion remains the mainstay of therapy, which may lead to iron overload causing severe complications and damage in different body organs (Martin 2013).

Long-term iron chelation is essential for people with thalassemia to minimize the ongoing iron loading process (Rachmilewitz 2011; Ware 2013). Three iron-chelating agents, deferoxamine, deferiprone, and deferasirox, are approved by the USA's Food & Drug Administration (FDA) and are commercially available. Routine monitoring may vary with different iron chelators and as a minimum should include serum ferritin levels (every three months) and measurements of cardiac and liver iron burden with annual magnetic resonance imaging (MRI) scans (Badawy 2016a; Martin 2013). Recent studies have shown the need for iron chelation therapies has an impact on the quality of life of people with thalassemia and results in low levels of personal satisfaction (Abetz 2010; Cappellini 2007; Payne 2008; Porter 2012; Taher 2010; Trachtenberg 2012a; Trachtenberg 2014). In addition, suboptimal adherence can increase adverse events associated with iron overload and result in increased morbidity, mortality, healthcare utilization and cost of care (DiMatteo 2002; Sabate 2003; Vekeman 2016).

Description of the intervention

Mobile technology interventions for promoting medication adherence and disease management include delivery of education, reminders, or behavioral skills through cell (mobile) phones (e.g. text-messaging and mobile applications), the Internet (e.g. web-based interventions), or other mobile technology tools. Mobile technology interventions could:

1. enhance the communication between patients and healthcare providers,

2. facilitate management and self-monitoring of thalassemia;
3. provide education about thalassemia, iron chelators and other related medications;
4. support adherence to iron chelators or medications using reminders;
5. offer a network for communication among patients with thalassemia;
6. support decision making for people with thalassemia and their parents or caregivers; or
7. collect or capture users' data (from the individuals concerned and their parents or caregivers).

We conducted a brief scoping review of the literature in PubMed and found two published studies that used mobile-based interventions to improve adherence to iron chelation in people with thalassemia (Leonard 2017; Ward 2016). The first study included 35 people with thalassemia (aged 18 to 34 years), who were part of a Delphi process to inform the development of a mobile app to improve disease self-management, including adherence to chelation therapy (Ward 2016). The research team was able to develop and test the mobile app with participants who perceived it as highly favorable with improved adherence to iron chelation and positive experience using it, especially the adherence pledge functionality and customized treatment goals (Ward 2016). The second study included 11 people (β -thalassemia major and sickle cell anemia) receiving chronic blood transfusions and evaluated a mobile app intervention as part of an intensive training program to improve disease self-management, including adherence to iron chelation therapy (Leonard 2017). The authors reported on the feasibility of the mobile app intervention and that there was high acceptability and improved disease knowledge, as well as adherence to iron chelation therapy (using medication possession ration with pharmacy records and laboratory markers of adherence) with serum ferritin levels trending downwards (Leonard 2017).

How the intervention might work

Mobile technology interventions for promoting medication adherence and disease management could:

1. enhance an individual's self-efficacy, organizational skills, or change adherence behavior (e.g. reminders for daily iron chelators, clinic appointment reminders, transfusion reminders, feedback on adherence to iron chelation therapy);
2. provide a form of communication (e.g. health professionals);
3. establish social support networks (e.g. advocacy groups, peer-to-peer networks); or
4. provide education about thalassemia, iron chelation therapy and necessary steps for optimal disease management.

By increasing self-efficacy (Bandura 1977) and providing support mechanisms (Christakis 2004; Cobb 1976; Cohen 1985), computer and mobile technology interventions may influence health behaviors and enhance self-management of long-term illnesses. These interventions may facilitate education on self-management problem solving skills, and in this way increase the individual's confidence in carrying out the behaviors necessary to achieve the desired goal of optimum disease management. A recently developed taxonomy of behavior change techniques (BCT) has been published with 93 consensually agreed, distinct BCTs, which

will help to further define specific intervention effects, including mobile technology interventions (Michie 2013).

Why it is important to do this review

Management of thalassemia represents a challenge for people with the disease and their families (Badawy 2016a; Evangeli 2010). Recent reports demonstrated a high prevalence of poor self-management and non-adherence in thalassemia in both children and adults (Cappellini 2007; Evangeli 2010; Haghpanah 2014; Lee 2011; Porter 2012; Porter 2011; Trachtenberg 2011; Vekeman 2016) similar to other chronic health conditions (Loiselle 2016; Modi 2012; Walsh 2014). Nevertheless, effective self-management is essential to maximize treatment efficacy, optimize clinical outcomes, and reduce unnecessary health care utilization and costs (Modi 2012). However, people with thalassemia and their families are responsible for managing complex and time-consuming treatment regimens, including daily medications (e.g. iron chelators, vitamins, hormonal supplements), laboratory monitoring (e.g. serum ferritin, hemoglobin concentration), imaging studies (e.g. MRI of liver R2*, MRI of heart T2*), and attendance at regular transfusions as well as routine clinic appointments with a variety of healthcare professionals (Badawy 2016a; Rachmilewitz 2011; Rund 2005). These treatment regimens could place substantial burden on individuals with thalassemia and their families, and effective management of these regimens represents a challenge to them. Moreover, in relation to industrialised countries, given that thalassemia predominantly affects individuals who are of ethnic minorities (Rund 2005; Weatherall 2012), disparities in access to care and resources may also serve as further barriers to effective self-management.

People with thalassemia and their families have adopted computer and mobile technology such as standard cell phones, smartphones, the Internet, and social networking at a rapid rate across levels of social position and status (Badawy 2016b; Lenhart 2015; Shah 2014; Smith 2015a; Ward 2016). Therefore, the widespread availability and frequent use of these technologies by those with thalassemia and their families across age groups present an opportunity to develop high-quality, efficacious, and cost-effective interventions to facilitate self-management, promote medication adherence, link people with thalassemia with their physicians, and improve health outcomes (Badawy 2016b; Leonard 2017; Shah 2014; Ward 2016). There has been growing interest and evidence to support the utilization of technology-based strategies, including mobile technology interventions, to improve medication adherence and self-management in people with chronic health conditions (Badawy 2017a; Badawy 2017b; Badawy 2017c; Badawy 2018; Bonoto 2017; de Jongh 2012; Gurol-Urganci 2013; Lin 2014; Liu 2014; Pfaeffli 2016; Smith 2015b; Thakkar 2016; Whitehead 2016) including sickle cell disease (Crosby 2017; Jonassaint 2015) and thalassemia (Leonard 2017; Ward 2016), though the cost-effectiveness of such interventions warrants further investigation (Badawy 2016c). To date, the evidence for the use of computer and mobile technology interventions in people with thalassemia remains unclear. Although this systematic review may not yet identify any eligible studies, it is important to identify and report this knowledge gap in the field of thalassemia to highlight where future research efforts can be directed using computer and mobile technology interventions.

OBJECTIVES

To identify and assess the effects of computer and mobile technology interventions designed to facilitate medication adherence and disease management in individuals with thalassemia, including:

1. evaluating the effects of using computer and mobile technology interventions for medication adherence and disease management on health and behavioral outcomes;
2. identifying and assessing the effects of computer and mobile technology interventions specific to different age groups (children, adolescents and adults) and type of modality (e.g. cell phone, the Internet).

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCT) and quasi-RCTs comparing single- or multi-component interventions versus no intervention, placebo or standard care. We also planned to include non-randomized studies of interventions (NRSI): controlled before-after (CBA) studies, and interrupted-time-series (ITS) studies. We used the Cochrane Effective Practice and Organization of Care (EPOC) Group's definition of study designs to consider studies for inclusion (EPOC 2017)*.

Given the growing evidence in the field and the possible paucity of research studies, in particular RCTs, evaluating technology interventions in this population, we wanted to broaden our eligibility criteria to be able to report the up-to-date current status of the field and identify gaps. Therefore, we planned to include NRSI in this review.

We planned to include cluster-RCTs, non-randomized cluster studies and CBA studies if they have at least two intervention sites and two control sites. However, we planned to exclude such studies with only one intervention or control site since the intervention (or comparison) could be confounded by the study site, thus making it difficult to attribute any observed differences to the intervention rather than to other site-specific variables (EPOC 2017).

We also planned to include ITS and repeated-measures studies which have a clearly defined point in time when the intervention occurred and at least three data points before and at least three data points after the intervention. We planned to exclude ITS studies that do not have a clearly defined point in time when the intervention occurred, fewer than three data points before and after the intervention, or if the ITS study has ignored secular (trend) changes, performed a simple t-test of the pre- versus post-intervention periods and re-analysis of the data is not possible (EPOC 2017).

We planned to evaluate for the possible bias introduced by confounding in the different types of included studies, and we will adjust for confounder variables. Possible confounders include age and education of the participant, self-management skills, personal behavior or personality traits, health literacy, parental involvement in medical care, parental education, household income, insurance status, access to healthcare services, type of thalassemia (TDT

versus NTD), associated co-morbidities or complications (or both) affecting clinical course, and iron chelation regimen.

We planned to exclude studies with a cross-over design since any intervention focused on improving disease knowledge will leave that knowledge with a residual 'carry-over' effect.

* Please refer to '[Differences between protocol and review](#)'.

Types of participants

People with TDT or NTD of all ages (children, adolescents and adults) or their parents or caregivers.

Types of interventions

Interventions delivered via cell phones (including smart phones), the Internet or other technology or mobile devices compared to other technology interventions or no interventions or standard of care or placebo.

We planned to include remote and Web 2.0-based interventions delivered via technologies that give people with thalassemia access to e-health information to promote medication adherence and disease management. These e-health technologies included personal computers (PCs) and applications (apps) for mobile technology such as iOS tablets (iPads), Android tablets and smartphones.

We planned to include e-health or technology-based interventions that are focused on people with thalassemia and parents or caregivers to promote individual medication adherence and disease management and are self-administered or user-centred (where the intervention design process focuses on user needs).

We also planned to include as possible comparison groups (whenever reported): face-to-face support; educational material (either as hard copy or digital documents); or self-management tools (either as hard copy or digital documents).

We planned to exclude studies that focus on monitoring devices, telemonitoring or telemedicine or other technologies that involve the participation of healthcare professionals.

Types of outcome measures

Primary outcomes

1. Medication adherence
 - a. directly observed adherence rates with individuals recording their daily iron chelator use on their cell phones
 - b. radiological markers of iron overload (MRI of liver R2* and MRI of heart T2*)
 - c. laboratory markers of iron overload (serum ferritin levels)
 - d. iron chelation adherence rates by pharmacy records (i.e. medication possession ratio)
 - e. self-reported iron chelator adherence rate

Secondary outcomes

1. Knowledge about thalassemia
2. Health outcomes (e.g. health-related quality of life)
3. User evaluation of the mobile technology interventions, including acceptability and satisfaction

4. Adverse events (e.g. issues of privacy and disclosure, or failure or delay in the intervention delivery)

Search methods for identification of studies

We searched for all relevant published and unpublished trials without restrictions on language, year or publication status.

Electronic searches

We searched the Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register using the terms: (thalassaemia OR (haemoglobinopathies AND general)) AND (mobile technology).

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library) and weekly searches of MEDLINE. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Public Health Agency Annual Scientific Meeting (formerly the Caribbean Health Research Council Meeting); and the National Sickle Cell Disease Program Annual Meeting. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's [website](#).

Date of the most recent search of the Haemoglobinopathies Trials Register: 20 June 2019.

In addition to the above, we conducted a search of the following databases:-

- CENTRAL, Other Reviews (DARE) and Technology Assessments (HTA) Databases (the Cochrane Library) (22 February 2018) (www.cochranelibrary.com/);
- PubMed (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, for recent records not yet added to MEDLINE) (22 February 2018) (www.ncbi.nlm.nih.gov/sites/entrez);
- MEDLINE (OvidSP, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE, 1946 to 22 February 2018);
- Embase (OvidSP, 1974 to 22 February 2018);
- CINAHL (EBSCOHost, 1937 to 22 February 2018);
- PsycInfo (EBSCOHost, 1900 to 22 February 2018);
- ProQuest Dissertations & Theses Global (ProQuest, 1861 to 22 February 2018);
- Web of Science & Social Sciences Conference Proceedings Indexes (CPSI-S & CPSSI, 1990 to 22 February 2018);
- Institute of Electrical and Electronics Engineers Explore (IEEE Xplore, 1963 to 22 February 2018).

Additionally, we searched the following trial databases for trials (22 February 2018):

- ISRCTN registry (www.isrctn.com/);
- ClinicalTrials.gov (www.ClinicalTrials.gov);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/).

See [Appendix 1](#) for the full search strategies.

Searching other resources

We aimed to further identify unpublished work by searching the abstract books of the International Society for Research on Internet interventions (ISRII); the NIH Wireless Health Conference; the Society for Behavioral Medicine (SBM) Annual Meeting; and the Connected Health Conference over the past 10 years (2007 to 2018).

Reference lists

The reference lists of all included articles and relevant systematic reviews were reviewed to identify any additional studies. We planned to contact the lead authors of the included studies to identify any unpublished material, missing data or information regarding ongoing relevant studies.

Data collection and analysis

Selection of studies

We selected studies according to chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Two review authors (SB and KM) independently screened all electronically derived citations and abstracts of papers identified by the search strategy for relevance. We excluded all articles that are clearly irrelevant at this stage based on the title and the abstract. Two review authors (SB and KM) independently assessed the full texts of all potentially relevant studies for eligibility against criteria outlined above. If a consensus could not be reached, we resolved any disagreements by discussion and consultation with a third review author (TP). We planned to seek further information from study authors if studies or abstracts contain insufficient data to make a decision about eligibility. We designed a study eligibility form which included ascertaining whether the participants have thalassaemia, if the study addressed mobile technology interventions to improve disease management, and whether the study was randomized or a NRSI or a CBA or an ITS study. We also recorded the reasons why potentially relevant studies failed to meet the eligibility criteria.

Data extraction and management

Two review authors (SB and KM) planned to conduct data extraction according to Cochrane guidelines (Higgins 2011a) and according to the criteria developed for NRSI as recommended in chapter 13 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2011). We aimed to resolve any disagreements by consensus. We planned to pilot data extraction forms for RCTs, NRSI or CBAs or ITS studies; thereafter, data extraction is planned to be conducted by two authors (SB and KM) independently for all the studies using templates modified to reflect the outcomes in this review. In addition, we planned to use the available tables in Review Manager 5 (RevMan 2014) to extract data on study characteristics as below.

General information

Review author's name, date of data extraction, study ID, first author of study, author's contact address (if available), citation of paper, and objectives of the study.

Study details

Study design, location, setting, sample size, power calculation, treatment allocation, inclusion and exclusion criteria, reasons for exclusion, comparability of groups, length of follow-up, stratification, stopping rules described, statistical analysis, results, conclusion, and funding.

Characteristics of participants

Age, gender, total number recruited, total number randomized, total number analyzed, types of underlying disease, loss to follow-up numbers, dropouts (percentage in each arm) with reasons, protocol violations (if any), and co-morbidities.

Interventions

Details of the mobile technology interventions including purpose (e.g. adherence promotion), modality used (cell phone, the Internet or other technology), length of intervention, how the intervention is being delivered (i.e. electronically only or electronically in addition to group, face-to-face, written information) and by whom (i.e. clinicians, researchers, patients or parents) and where the intervention is being delivered (i.e. hospital, clinic, home or other settings). We planned to analyse data from different modes of interventions separately (e.g. cell phone versus standard care, Internet versus standard care, etc.).

Outcomes measured

Data on measures of medication adherence, including iron chelation adherence rates by self-report or pharmacy records (or both) (i.e. medication possession ratio), laboratory markers of iron overload (serum ferritin level), radiological markers of iron overload (MRI of liver R2* and MRI of heart T2*), and other reported adherence indicators; also data on knowledge about thalassaemia and health outcomes (e.g. health-related quality of life).

Data on user perception of acceptability and satisfaction (e.g. the Likert ratings of satisfaction). Adverse events if reported and whether or not they were associated with interventions.

For NRSI, CBA or ITS studies, data on: confounding factors; the comparability of groups on confounding factors; methods used to control for confounding and on multiple effect estimates (both unadjusted and adjusted estimates) as recommended in chapter 13 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2011). We used both full-text versions and abstracts as data sources and we used one data extraction form for each unique study. Where sources did not provide sufficient information, we planned to contact authors and study groups for additional details. We planned for one review author to enter data and for a second to check these data for accuracy.

Assessment of risk of bias in included studies

In future, two review authors (SB and KM) will assess included studies for possible risks of bias as described in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011c). In our assessment, we will include information about the design, the conduct and the analysis of the study.

RCTs

We planned to assess each criterion using Cochrane's RoB (V2.0) tool for assessing the risk of bias for RCTs (classified as 'low risk', 'high

risk' or 'some concerns' for bias) in the following areas (Higgins 2011c).

Bias arising from the randomization process

1. Was the allocation sequence random?
2. Was the allocation sequence concealed until participants were recruited and assigned to interventions?
3. Were there baseline imbalances that suggest a problem with the randomization process?
4. What is the predicted direction of bias arising from the randomization process?

Bias due to deviations from intended interventions

1. Were participants aware of their assigned intervention during the RCT?
2. Were carers and trial personnel aware of participants' assigned intervention during the RCT?
3. Were there deviations from the intended intervention beyond what would be expected in usual practice?
4. Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?
5. Were any participants analysed in a group different from the one to which they were assigned?
6. Was there potential for a substantial impact (on the estimated effect of intervention) of analysing participants in the wrong group?
7. What is the predicted direction of bias due to deviations from intended interventions?

Bias due to missing outcome data

1. Were outcome data available for all, or nearly all, participants randomized?
2. Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?
3. Is there evidence that results were robust to the presence of missing outcome data?
4. What is the predicted direction of bias due to missing outcome data?

Bias in measurement of the outcome

1. Were outcome assessors aware of the intervention received by participants?
2. Was the assessment of the outcome likely to be influenced by knowledge of intervention received?
3. What is the predicted direction of bias due to measurement of the outcome?

Bias in selection of the reported result(s)

1. Are the reported outcome data likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? Or from multiple analyses of the data?
2. What is the predicted direction of bias due to selection of the reported result?

Overall bias

An overview of the overall bias identified.

NRSI studies

We planned to use the ROBINS-I tool (Risk Of Bias In Non-randomized Studies of Interventions) to rate the quality of NRSI or CBA studies (Sterne 2016). The ROBINS-I tool uses signalling questions and covers seven domains (listed below) where the quality of evidence is rated as 'low', 'moderate', 'serious', 'critical' or 'no information'.

Bias due to confounding

1. Is there potential for confounding of the effect of intervention in this study?
2. Was the analysis based on splitting participants' follow-up time according to intervention received?
3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?
4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?
5. Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?
6. Did the authors control for any post-intervention variables that could have been affected by the intervention?
7. Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time varying confounding?
8. Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?

Bias in the selection of participants into the study

1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?
2. Were the post-intervention variables that influenced selection likely?
3. Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?
4. Do start of follow-up and start of intervention coincide for most participants?

Bias in classification of interventions

1. Were intervention groups clearly defined?
2. Was the information used to define intervention groups recorded at the start of the intervention?
3. Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?
4. What is the predicted direction of bias due to measurement of outcomes or interventions?

Bias due to deviation from intended interventions

1. Were there deviations from the intended intervention beyond what would be expected in usual practice?
2. Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?
3. Were important co-interventions balanced across intervention groups?
4. Was the intervention implemented successfully for most participants?

5. Did study participants adhere to the assigned intervention regimen?
6. Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?
7. What is the predicted direction of bias due to deviations from the intended interventions?

Bias due to missing data

1. Were outcome data available for all, or nearly all, participants?
2. Were participants excluded due to missing data on intervention status?
3. Were participants excluded due to missing data on other variables needed for the analysis?
4. Are the proportion of participants and reasons for missing data similar across interventions?
5. Is there evidence that results were robust to the presence of missing data?
6. What is the predicted direction of bias due to missing data?

Bias in measurement of outcomes

1. Could the outcome measure have been influenced by knowledge of the intervention received?
2. Were outcome assessors aware of the intervention received by study participants?
3. Were the methods of outcome assessment comparable across intervention groups?
4. Were any systematic errors in measurement of the outcome related to intervention received?
5. What is the predicted direction of bias due to measurement of outcomes?

Bias in the selection of the reported result

1. Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain? Or from multiple analyses of the intervention outcome relationship? Or from different subgroups?
2. What is the predicted direction of bias due to selection of the reported result?

ITS studies

For ITS studies, we planned to use the risk of bias criteria below as suggested for EPOC reviews (EPOC 2017) as follows.

1. Was the intervention independent of other changes?
2. Was the shape of the intervention effect pre-specified?
3. Was the intervention unlikely to affect data collection?
4. Was knowledge of the allocated interventions adequately prevented during the study?
5. Were incomplete outcome data adequately addressed?
6. Was the study free from selective outcome reporting?
7. Was the study free from other risks of bias?

We planned to resolve disagreements on the assessment of quality of an included study by discussion until consensus is reached or by consultation with a third review author (TP).

Measures of treatment effect

RCTs

We planned to report the following continuous primary endpoints of medication adherence, including iron chelation adherence rates by self-report or pharmacy records (i.e. medication possession ratio), laboratory markers of iron overload with serum ferritin level, radiological markers of iron overload (MRI of liver R2* and MRI of heart T2*), and other reported adherence indicators. We also planned to report the following continuous secondary endpoints (user evaluation of acceptability and satisfaction).

For continuous endpoints, we planned to extract and report the absolute change from baseline using statistical analysis, adjusting for baseline differences, in both the treatment and control groups. We planned to record the mean, standard deviation (SD) and total number of participants in both the treatment and control groups. For those using the same scale or outcome, we planned to perform analyses using the mean difference (MD) with 95% confidence intervals (CIs). For those reported using different scales or outcomes, we planned to use the standardized mean difference (SMD). We planned to extract and report the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute post-intervention difference between the intervention and control groups, as well as the absolute pre-intervention difference between the intervention and control groups divided by the post-intervention level in the control group) (EPOC 2017).

For binary outcomes we planned to record the number of events and the total number of participants in both the treatment and control groups and report the pooled risk ratio (RR) with a 95% CI (Deeks 2011). Where the number of observed events was small (less than 5% of sample per group), and where studies have balanced treatment groups, we planned to report the Peto odds ratio (OR) with 95% CI (Deeks 2011).

For cluster-RCTs, we planned to extract and report direct estimates of the effect measure (e.g. RR with a 95% CI) from an analysis that accounts for the clustered design. We planned to obtain statistical advice to ensure the analysis is appropriate. If appropriate analyses are not available, we planned to make every effort to approximate the analysis with necessary adjustment using effective sample size recalculation, following the recommendations in chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d).

We planned to undertake quantitative assessments using the Review Manager (RevMan) software (RevMan 2014), if data allowed.

NRSI studies

For continuous variables in any included studies, if available, we planned to extract and report the absolute change from baseline using statistical analysis, adjusting for baseline differences (such as regression models, mixed models or hierarchical models). An adjusted change of outcomes was required in NRSI and confounding was considered and evaluated in the included articles. If available, we planned to extract and report the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute post-intervention difference between the intervention and control groups, as well as the absolute pre-intervention difference between the intervention and control groups divided by the post-intervention level in the control group) (EPOC 2017).

For binary outcomes, if available we planned to extract and report the RR with a 95%CI from statistical analyses, adjusting for baseline differences (such as Poisson regressions or logistic regressions) or the ratio of RRs (i.e. the RR post intervention / risk ratio pre intervention).

ITS studies

For ITS studies that fulfil the criteria of analysis, and from which relevant information can be extracted, we planned to standardize data by dividing the level (or time slope) and standard error (SE) by the SD of the pre-intervention slope, in order to obtain the effect sizes. Where appropriate, we planned to report the number-needed-to-treat-to-benefit (NNTB) and the number-needed-to-treat-to-harm (NNTH) with 95% CIs. If we were not able to report the available data in any of the formats described above, we planned to produce a narrative report, and if appropriate, we planned to present the data in tables.

Unit of analysis issues

We planned to identify issues related to unit of analysis, given the inclusion of cluster-RCTs or non-randomized studies, and multiple observations for the same outcome. Therefore, if any of these study designs included in our review, we planned to treat these in accordance with the advice given in chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d). For cluster designs, we planned to extract results adjusted for clustering, and if analyses have not been adjusted for clustering, we planned to re-analyze the data taking clustering and individual participant data (IPD) into account, if possible; if not possible, we planned to present data in a table. If participants were randomized more than once, we planned to contact the authors of the study to provide us with data on outcomes associated with the initial randomization. For studies with multiple treatment groups we planned to include subgroups that were considered relevant to the analysis. When appropriate, we planned to combine groups to create a single pair-wise comparison. If not possible, we planned to select the most appropriate pair of interventions and exclude the others (Higgins 2011d). We planned to deal with any unit of analysis issues arising from the inclusion of ITS studies according to the EPOC recommendations (EPOC 2017). We planned to analyze ITS studies as a statistical comparison of time trends before and after the intervention. In time-series analysis, there are a number of statistical techniques that could be used depending on the characteristics of the data, the number of data points available and whether autocorrelation was present (e.g. auto-regressive integrated moving average 'ARIMA' model).

Dealing with missing data

If we identified incidences where we suspected data were missing or unclear, we planned to contact study authors directly. We planned to record the number of participants lost to follow-up for each study. Where possible, we planned to analyze data on an intention-to-treat (ITT) basis, but if insufficient data had been available, we planned to present per protocol analyses (Higgins 2011c).

Assessment of heterogeneity

If the clinical and methodological characteristics of individual studies are sufficiently homogeneous, we planned to combine the data to perform a meta-analysis. We planned to analyze

the data from RCTs, NRSI, CBA and ITS studies separately. We planned to assess the statistical heterogeneity of treatment effects between studies using a Chi² test with a significance level at $P < 0.1$. We planned to use the I² statistic to quantify the degree of potential heterogeneity and classify it as moderate if I² is greater than 50%, or considerable if I² is greater than 75%. If statistical heterogeneity is moderate within the studies selected for inclusion; in such cases, we planned to use the random-effects model. If statistical heterogeneity is considerable within the studies selected for inclusion, we planned not to report the overall summary statistic. When possible, we planned to assess the potential causes of heterogeneity by sensitivity and subgroup analyses (Deeks 2011).

Assessment of reporting biases

Where we identified at least 10 studies for inclusion in a meta-analysis, we planned to explore potential publication bias with a funnel plot and using a linear regression test. We planned to consider a P value of less than 0.1 as significant for this test (Sterne 2011).

Data synthesis

If studies were sufficiently homogenous in their study design, we planned to conduct a meta-analysis according to Cochrane recommendations (Deeks 2011). We planned to analyze RCTs and non-RCTs separately using the random-effects model as the true effects are expected to be related but not the same for included studies. If we cannot perform a meta-analysis, we planned to include a narrative describing the results and the results from all studies presented in the tables.

For RCTs, where meta-analysis was feasible, we planned to use the inverse variance method for continuous outcomes, or outcomes that included data from cluster-RCTs. If we found heterogeneity to be above 75%, and we identified a possible cause for the heterogeneity, we planned to investigate these with subgroup analyses. If a cause for the heterogeneity cannot be found, then we planned not to perform a meta-analysis.

If meta-analysis was feasible for NRSI or CBA studies, we planned to analyze these separately. We planned only to analyze outcomes with adjusted effect estimates, if these are adjusted for the same factors using the inverse variance method as recommended in chapter 13 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2011).

If meta-analysis was feasible for ITS studies, we planned to use the effect sizes (if reported in the included studies or obtained, as described earlier) and we planned to pool these using the generic inverse variance method in RevMan (RevMan 2014).

We planned to report data for our listed outcomes at the following time points: pre-intervention; immediate post-intervention; and at first follow-up (up to 12 months).

Subgroup analysis and investigation of heterogeneity

If adequate data were available, we planned to perform subgroup analyses according to Cochrane recommendations (Deeks 2011) for each of the following criteria, and separately for the different study design types included in the review in order to assess the effect on heterogeneity. We planned to base the subgroup analyses on:

1. delivery mode, phone-based versus Internet-based interventions;
2. age groups, children (8 to 11 years old) (parent-focused) versus adolescents (12 to 17 years old) versus adults (18 years and above);
3. transfusion-dependent versus non-transfusion-dependent thalassemia; and
4. iron-chelation regimen, deferasirox versus deferoxamine versus deferiprone.

Sensitivity analysis

We planned to assess the robustness of the review findings by performing the following sensitivity analyses according to Cochrane recommendations where appropriate (Deeks 2011):

1. including only those studies with a 'low' risk of bias (e.g. RCTs with methods assessed as low risk for random sequence generation and concealment of treatment allocation);
2. including only those studies with less than a 20% dropout rate.

Summary of findings table

We plan to use the GRADE approach to generate a 'Summary of Findings' table as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a). We will rate the quality of the evidence as 'high', 'moderate', 'low', or 'very low' using the five GRADE considerations.

1. Risk of bias (serious or very serious)
2. Inconsistency (serious or very serious)
3. Indirectness (serious or very serious)
4. Imprecision (serious or very serious)
5. Publication bias (likely or very likely)

For non-RCTs or CBA or ITS studies, we will also consider the following factors:

1. dose response (yes or no);
2. size of effect (large or very large);
3. confounding either reduces the demonstrated effect or increases the effect if no effect was observed (yes or no).

When using GRADE, we planned to initially rate NRSI or CBA or ITS studies as low quality and upgrade according to GRADE guidelines if appropriate. We planned to present the outcomes for these studies in separate tables from outcomes for the results of RCTs. We planned to report the following outcomes in each 'Summary of findings' table:

1. directly observed adherence rates with individuals recording their daily iron chelator use on their cell phones;
2. radiological markers of iron overload (MRI of liver R2* and MRI of heart T2*);
3. laboratory markers of iron overload (serum ferritin levels);
4. iron chelation adherence rates by pharmacy records (i.e. medication possession ratio);
5. self-reported iron chelation adherence rate;
6. disease knowledge about thalassemia; and
7. health outcomes (e.g. health-related quality of life).

RESULTS

Description of studies

See Characteristics of included studies; [Characteristics of excluded studies](#).

Results of the search

See PRISMA flow diagram ([Figure 1](#)).

Figure 1. Study flow diagram.

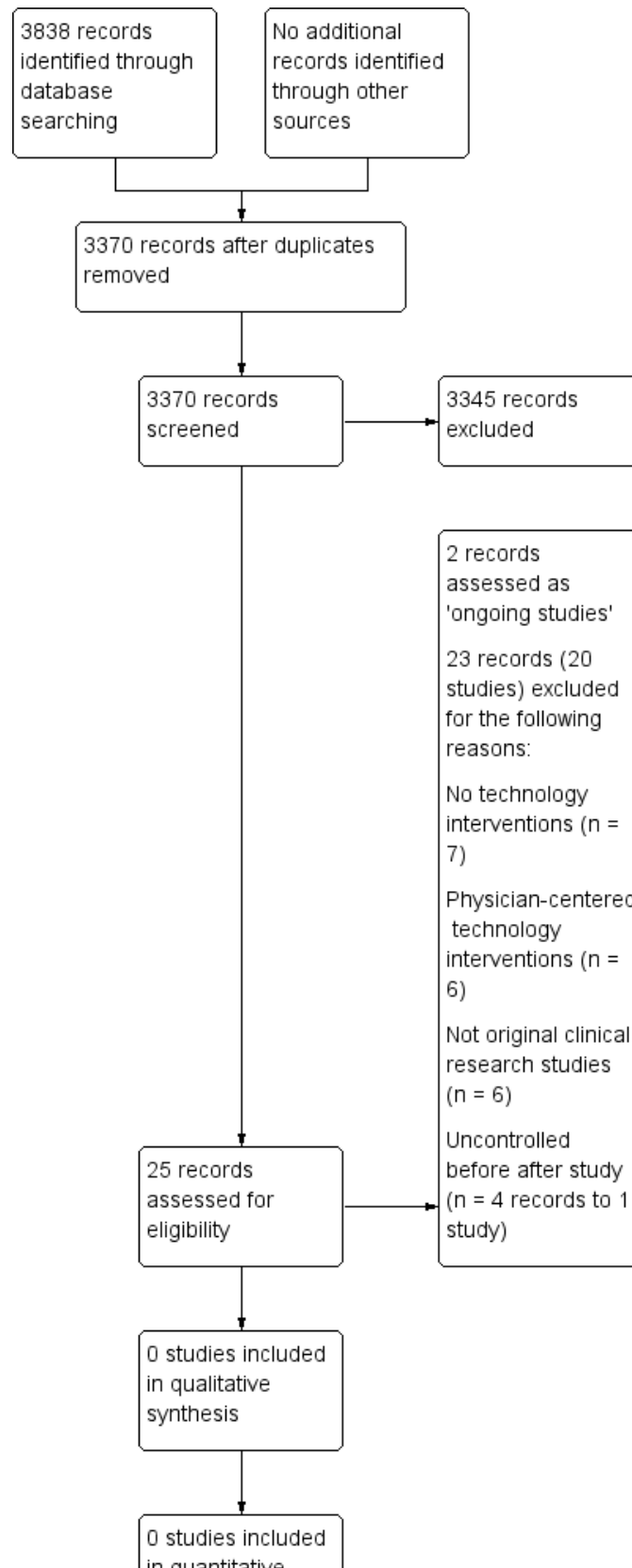


Figure 1. (Continued)

0 studies included in quantitative synthesis (meta-analysis)

In the searches for this review we identified a total of 3838 potentially relevant references. There were 3370 references after we removed duplicates and two review authors (SB and KM) excluded 3345 references on the basis of the title and the abstract. Two authors (SB and KM) reviewed 25 references for relevance. We did not identify any completed NRSI or any RCTs, cluster-RCTs, CBA or ITS studies that met the inclusion criteria. We have listed two RCTs as ongoing studies and we excluded 20 studies (23 references) that did not meet our pre-defined inclusion criteria. We resolved disagreements by discussion and consultation with a third senior review author (TP).

Included studies

No studies were identified for inclusion in the review.

Excluded studies

We excluded 20 studies after full-text screening for the following reasons. Six studies did not use technology interventions (Abu Samra 2015; Dehkordi 2008; Gambari 2007; Olivieri 1991; Paholpak 2006; Trachtenberg 2012b). Six studies used physician-centered technology interventions, defined as interventions developed for physicians or other healthcare providers to enhance their communications with patients and families or documentation of their medical evaluation and management, such as electronic health records (Antonioni 2015; Arbaify 2017; Deftereos 2001; Lederer 2009; Piga 2013; Santini 2017). Six studies were not original clinical research studies (Bal 2014; Bobati 2016; Jonassaint 2012; Nawaz 2012; Paokanta 2014; Yamashita 1998). Two studies were an inappropriate design, uncontrolled before after pilot study (Leonard 2017) and intervention development and usability pilot study (Ward 2016).

Ongoing studies

We identified two ongoing RCTs that we plan to assess in a future update (IRCT20170826035907N1; IRCT20180207038655N1).

Risk of bias in included studies

No studies were identified for inclusion in the review.

Effects of interventions

No studies were identified for inclusion in the review.

DISCUSSION

For people with thalassemia, long-term RBC transfusion remains the mainstay of therapy. This may lead to iron overload causing severe complications and damage in different body organs, with the heart, liver and endocrine glands being particularly vulnerable. Using data from six state Medicaid programs (1997 to 2013), a recent research study has shown that adherence to iron chelation ranges from 20% to 66% in people with thalassemia, which varies based on the type of iron chelator (Vekeman 2016). Similar data were recently

reported in two systematic reviews for iron chelation adherence rates in people with sickle cell disease, 22% to 89% (Loiselle 2016) and 16% to 89% (Walsh 2014).

We identified two published studies that used mobile-based interventions to improve adherence to iron chelation in people with thalassemia (Leonard 2017; Ward 2016). The Ward study included 35 people with thalassemia (aged 18 to 34 years), who were part of a Delphi process to inform the development of a mobile app to improve disease self-management, including adherence to chelation therapy (Ward 2016). The research team was able to develop and test the mobile app with participants who perceived it as highly favorable with improved adherence to iron chelation and positive experience using it, especially the adherence pledge functionality and customized treatment goals (Ward 2016). The Leonard study included 11 people (β-thalassemia major and sickle cell anemia) receiving chronic blood transfusions and evaluated a mobile app intervention as part of an intensive training program to improve disease self-management, including adherence to iron chelation (Leonard 2017). The authors reported on the feasibility of the mobile app intervention and that there was high acceptability and improved disease knowledge, as well as adherence to iron chelation (using medication possession ratio with pharmacy records and laboratory markers of adherence) with serum ferritin levels trending downwards (Leonard 2017). However, these two studies were not included in this review because of inappropriate design, uncontrolled before after pilot study (Leonard 2017) and intervention development and usability pilot study (Ward 2016).

Summary of main results

We found no evidence in the form of RCTs, cluster-RCTs, CBA or ITS studies that met the inclusion criteria. We identified two ongoing RCTs that will be assessed further in a future update of this review.

Overall completeness and applicability of evidence

This review provides the most up-to-date assessment of the evidence for computer and mobile technology interventions designed to promote adherence to iron chelation therapy and disease management in people with thalassemia. The results of this review should be interpreted with caution and only in consideration of the following factors.

1. We did not identify any RCTs, cluster-RCTs, CBA or ITS studies that met the inclusion criteria; we identified two ongoing RCTs that may be eligible in a future update of this review.
2. Due to lack of evidence, this review cannot comment on the efficacy or effectiveness of computer and mobile technology intervention strategies to promote disease management and adherence to iron chelation therapy in people with thalassemia.

Quality of the evidence

No studies were identified for inclusion in the review.

Potential biases in the review process

To our knowledge, our review process was free from bias. We conducted a comprehensive search: searching data sources (including multiple databases, and clinical trial registries) to ensure that all relevant studies would be captured. We had no restrictions for the language in which the paper was originally published. We carefully evaluated the relevance of each potentially-eligible paper.

Agreements and disagreements with other studies or reviews

There have been limited data from published intervention studies to address adherence to iron chelation or disease management in people with thalassemia.

A study by Bahnasawy evaluated the effect of an intervention with clinical pharmacist services, including detection of drug-related problems and their management, education about β -thalassemia and iron chelators, and individually-tailored medication charts, compared to standard of care in 48 people with β -thalassemia (Bahnasawy 2017). At six months follow-up, the authors reported a significant improvement in adherence to iron chelator therapy, in serum ferritin as a marker of iron overload, in participants' satisfaction and in quality of life, with fewer drug-related problems in the intervention arm compared to the control arm (Bahnasawy 2017).

Pakbaz examined the impact of providing patient education about iron overload with assessment of adherence to iron chelation therapy (subcutaneous deferoxamine injections) using the numerical Likert Scale and liver iron concentration or overload status using SQUID biosusceptometer (Pakbaz 2005). The authors showed improvement in self-report adherence rates to iron chelation therapy as well as liver iron concentration at 15 months follow-up (Pakbaz 2005).

Koch evaluated the effect of contingency contracting with 23 people with β -thalassemia as an intervention to improve their adherence level to iron chelation therapy (subcutaneous deferoxamine injections) and measured adherence by counting the number of empty vials (Koch 1993). At six months follow-up, the authors reported success of the contingency contracting program with improvement in adherence rates in majority of participants.

Treadwell examined the impact of participating in Desferal or Deferoxamine Day Camp with educational strategies and peer support as an intervention to improve self-management skills in 15 individuals with β -thalassemia or sickle cell disease and their caregivers (Treadwell 2001). The authors showed adherence to iron chelation at follow-up (i.e. number of days of deferoxamine administration) was associated with perceived level of support as well as patient and caregiver disease knowledge. The authors also reported that increased disease knowledge as well as shared responsibilities for care of home between patients and their caregivers have been associated with an improvement in markers of iron overload with lower serum ferritin and liver iron concentration (Treadwell 2001).

Further, a recent Cochrane Review identified no published data on psychological therapies for people with thalassemia as interventions to improve their ability to cope and self-manage their condition, or improve both medical and psychosocial outcomes (Anie 2014).

Another Cochrane Review showed very limited evidence to suggest indications that mobile phone messaging interventions may be beneficial in promoting self-management in people with chronic illnesses (de Jongh 2012). Similarly, Badawy has systematically evaluated the effects of text messaging and mobile phone apps as interventions to improve adherence to preventive behavior and to chronic medication regimens in adolescents (Badawy 2017a; Badawy 2017b). The authors reported significant improvement in adherence with moderate effect sizes, although most of the included studies were of low or moderate quality (Badawy 2017a; Badawy 2017b). Furthermore, Thakkar conducted a meta-analysis of RCTs to assess the effect of mobile phone text messaging interventions on medication adherence in chronic disease (Thakkar 2016). The authors found that these interventions increased the odds of medication adherence by approximately two-fold, with about an 18% increase in adherence rates; however, most were of short duration and used self-report measures of medication adherence (Thakkar 2016).

AUTHORS' CONCLUSIONS

Implications for practice

Optimal disease management and adherence to iron chelation regimens can reduce morbidity and mortality in people with thalassaemia. Iron chelation regimens are not without side effects, which could reduce adherence levels. Evidence from other systematic reviews have identified several effective intervention strategies for promoting disease management and medication adherence, particularly in people with chronic medical conditions. In this review, we did not identify any randomized controlled trials (RCTs), cluster-RCTs, controlled before-after studies or interrupted-time-series studies that met the inclusion criteria. Therefore, well-designed clinical trials are needed to evaluate the successful translation of these intervention strategies to iron chelation regimens and disease management in this population.

Implications for research

Due to lack of evidence, we cannot comment on the efficacy or effectiveness of computer and mobile technology intervention strategies to promote disease management and adherence to iron chelation therapy in people with thalassemia. This limited evidence suggests that investigators need to be encouraged to develop and evaluate mobile technology interventions using various early-phase behavioral intervention study designs with small available samples. For example, rigorous single-study designs, mixed-methods designs, fidelity, and pilot-feasibility studies would help to optimize intervention development and pave the way for later efficacy studies (Czajkowski 2015).

In the future, RCTs will be needed to examine the efficacy of these interventions for improving adherence rates and disease management in this population. In addition, high-quality, non-randomized studies of interventions that measure adherence to iron chelation therapy before and after an intervention, over multiple time points, or in multiple settings could help to identify

evidence-based strategies that promote disease management and adherence to iron chelation regimens in people with thalassemia. Additionally, multi-modal assessment of adherence to iron chelation regimens using valid and reliable commonly used tools are essential to accurately assess the effects of an intervention, particularly in relation to quality of life, patient-reported outcomes, other health outcomes, morbidity and mortality. Finally, targeted strategies for different age groups, especially adolescents, are warranted.

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REFERENCES

References to studies excluded from this review

Abu Samra 2015 {published data only}

Abu Samra O, Auda W, Kamhaway H, Al-Tonbary Y. Impact of educational programme regarding chelation therapy on the quality of life for B-thalassemia major children. *Hematology* 2015;**20**(5):297-303.

Antoniou 2015 {published data only}

Antoniou Z, Schiza EC, Neokleous K, Angastiniotis M, Pattichis CS, Schizas CN. eHealth Services for the European Reference Network on Rare Anaemias (eENERCA). *Studies in Health Technology and Informatics* 2015;**213**:153-6.

Arbaiy 2017 {published data only}

Arbaiy N, Sulaiman SE, Hassan N, Afip ZA. Integrated Knowledge Based Expert System for Disease Diagnosis System. *IOP Conference Series: Materials Science and Engineering* 2017;**226**.

Bal 2014 {published data only}

Bal P, Shamsir S, Wand N, Yahya A, Yunus J, Supriyanto E, et al. MHealth Application: Mobile Thalassemia Patient Management Application. IEEE Conference on Biomedical Engineering and Sciences (IECBES), Kuala Lumpur, Malaysia. 2014:792-6.

Bobati 2016 {published data only}

Bobati SS, Viragi SV. Implementation of upgraded technology in the management of thalassaemic patients-an excellent response covering 14 districts Of North Karnataka. *Indian Journal of Hematology and Blood Transfusion* 2016;**32**:S483-S484.

Deftereos 2001 {published data only}

Deftereos S, Lambrinoudakis C, Andriopoulos P, Farmakis D, Aessopos A. A Java-based electronic healthcare record software for beta-thalassaemia. *Journal of Medical Internet Research* 2001;**3**:E33.

Dehkordi 2008 {published data only}

Dehkordi AH, Heydarnejad MS. Effect of booklet and combined method on parents' awareness of children with beta-thalassemia major disorder. *Journal of the Pakistan Medical Association* 2008;**58**(9):485-7.

Gambari 2007 {published data only}

Gambari R, Di Paola ML, Kleanthous M. Thalassemia on the WEB: From laboratory research to e-dissemination. *Minerva Biotechnologica* 2007;**19**:117-22.

Jonassaint 2012 {published data only}

Jonassaint J, De Castro LM. Information technology use by patients with hemoglobinopathies. *Blood* 2012;**120**(21). [Abstract No.: 4698]

Lederer 2009 {published data only}

Lederer CW, Basak AN, Aydinok Y, Christou S, El-Beshlawy A, Eleftheriou, A, et al. An electronic infrastructure for research and treatment of the thalassemiias and other hemoglobinopathies: the Euro-mediterranean ITHANET project. *Hemoglobin* 2009;**33**(3):163-76.

Leonard 2017 {published data only}

Leonard S, Anderson LM, Jonassaint J, Jonassaint C, Shah N. Utilizing a novel mobile health "Selfie" application to improve compliance to iron chelation in pediatric patients receiving chronic transfusions. *Journal of Pediatric Hematology/Oncology* 2017;**39**(3):223-9.

Leonard S, Jonassaint J, Anderson L, Shah N. The use of mobile technology for intensive training in medication management in the pediatric population. *Blood* 2014;**124**(21). [Abstract No.: 4842]

Leonard S, Jonassaint J, Anderson L, Shah N. The use of mobile technology to provide intensive training for oral chelation management in pediatric sickle cell disease and beta-thalassemia. *Pediatric Blood and Cancer* 2015;**62**:S47-S48.

Leonard S, Jonassaint J, Anderson L, Shah N. Use of Mobile Technology for Intensive Training in Medication Management. <https://clinicaltrials.gov/ct2/show/NCT02133560> (accessed 28 May 2019).

Nawaz 2012 {published data only}

Nawaz F, Gilmore A, Naorose-Abidi S, Cho G. Haemoglobinopathy patient access to modern communication technology: The feasibility of alternative communication strategies to manage clinic appointments. *Haematologica* 2012;**97**(Suppl 1):388. [Abstract No.: 0938]

Olivieri 1991 {published data only}

Olivieri NF, Matsui D, Hermann C, Koren G. Compliance assessed by the Medication Event Monitoring System. *Archives of Disease in Childhood* 1991;**66**(12):1399-402.

Paholpak 2006 {published data only}

Paholpak S, Jetsrisuparb A, Wiangnon S, Sangsahachat D, Padtawaro LO. Result of video-education on "genetic transmission in thalassemia" to thalassaemic patients and their parents. *Journal of the Medical Association of Thailand* 2006;**89**(11):1909-14.

Paokanta 2014 {published data only}

Paokanta P, Harnpornchai N, Cecarelli M, Vivas C, Sequeira P. A Knowledge Creation Innovation for Web-Knowledge-Base System Using Knowledge Management, and Data and Knowledge Engineering. Proceedings of the European Conference on Knowledge Management (ECKM), Santarem, Portugal. 2014; Vol. 3:1255-64.

Piga 2013 {published data only}

Piga A, Longo F, Musallam KM, Cappellini MD, Forni GL, Quarta G, et al. Assessment and management of iron overload in beta-thalassaemia major patients during the 21st century: a real-life experience from the Italian WEBTHAL project. *British Journal of Haematology* 2013;**161**(6):872-83.

Santini 2017 {published data only}

Santini S, Pescapé A, Valente AS, Abate V, Improta G, Triassi M, et al. Using fuzzy logic for improving clinical daily-care of β -

thalassemia patients. IEEE International Conference on Fuzzy Systems (FUZZ-IEEE), Naples, Italy. 2017:1-6.

Trachtenberg 2012b {published data only}

Trachtenberg FL, Martin M, Green S, Oliveros O, Carson S, Gerstenberger E, et al. Use of electronic data collection to assess pain in thalassaemia: a feasibility study. *International Journal of Palliative Nursing* 2012;**18**(9):441-5.

Ward 2016 {published data only}

Ward R, Taha KM. Patient involvement as experts in the development and assessment of a smartphone app as a patient education tool for the management of thalassaemia and iron overload syndromes. *Hemoglobin* 2016;**40**(5):323-9.

Yamashita 1998 {published data only}

Yamashita RC, Quirolo K, Choy J, Foote D. From a distance: using information technologies to overcome geographic boundaries in thalassaemia service delivery. *Annals of the New York Academy of Sciences* 1998;**850**:518-20.

References to ongoing studies

IRCT20170826035907N1 {published data only}

IRCT20170826035907N1. The effect of self-caring using Tele-Nursing on thalassaemia teenagers self-efficacy [Determining effect of self-caring using Tele-Nursing on major thalassaemia teenagers self-efficacy]. www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT20170826035907N1 (first received 01 January 2018).

IRCT20180207038655N1 {published data only}

IRCT20180207038655N1. The effect of mobile phone-based education on patients with thalassaemia [The Effect of Mobile Phone-Based Education for Improving Stress, Anxiety, Depression and Pain of Patients with Beta Thalassaemia Major]. www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT20180207038655N1 (first received 11 March 2018).

Additional references

Abetz 2010

Abetz L, Baladi JF, Jones P, Rofail D. The impact of iron overload and its treatment on quality of life: results from a literature review. *Health and Quality of Life Outcomes* 2006;**4**:73.

Angelucci 2010

Angelucci E. Hematopoietic stem cell transplantation in thalassaemia. *Hematology: The Education Program of the American Society of Hematology* 2010;**1**:456-62.

Anie 2014

Anie, K.A, Massaglia. P. Psychological therapies for thalassaemia. *Cochrane Database of Systematic Reviews* 2014, Issue 3. [DOI: [10.1002/14651858.CD002890.pub2](https://doi.org/10.1002/14651858.CD002890.pub2)]

Badawy 2016a

Badawy SM, Thompson AA. Management challenges in thalassaemia. In: Abutalib SA, Connors JM, Ragni MV editor(s). *Nonmalignant Hematology, Expert Clinical Review: Questions*

and Answer. Springer International Publishing, Switzerland, 2016.

Badawy 2016b

Badawy SM, Thompson AA, Liem RI. Technology access and smartphone app preferences for medication adherence in adolescents and young adults with sickle cell disease. *Pediatric Blood & Cancer* 2016;**63**(5):848-52.

Badawy 2016c

Badawy SM, Kuhns LM. Economic evaluation of text-messaging and smartphone-based Interventions to improve medication adherence in adolescents with chronic health conditions: a systematic review. *JMIR Mhealth and Uhealth* 2016;**4**(4):e121.

Badawy 2017a

Badawy SM, Kuhns LM. Texting and mobile phone app interventions for improving adherence to preventive behavior in adolescents: a systematic review. *JMIR Mhealth and Uhealth* 2017;**5**(4):e50.

Badawy 2017b

Badawy SM, Sinno MG, Kaviani S, O'Dwyer L, Kuhns LM. Text messaging and smartphone app interventions to improve medication adherence in adolescents with chronic conditions: a systematic review. *JMIR Mhealth and Uhealth* 2017;**5**(5):e66.

Badawy 2017c

Badawy SM, Thompson AA, Kuhns LM. Medication Adherence and Technology-Based Interventions for Adolescents With Chronic Health Conditions: A Few Key Considerations. *JMIR Mhealth Uhealth* 2017;**5**(12):e202.

Badawy 2018

Badawy SM, Cronin RM, Hankins J, Crosby L, DeBaun M, Thompson AA, Shah N. Patient-Centered eHealth Interventions for Children, Adolescents, and Adults With Sickle Cell Disease: Systematic Review. *Journal of Medical Internet Research* 2018;**20**(7):e10940.

Bahnasawy 2017

Bahnasawy SM, El Wakeel LM, Beblawy NE, El-Hamamsy M. Clinical pharmacist-provided services In iron-overloaded beta-thalassaemia major children: a new insight Into patient care. *Basic Clinical & Pharmacology & Toxicology* 2017;**120**(4):354-9.

Bandura 1977

Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychological Review* 1977;**84**(2):191-215.

Bonoto 2017

Bonoto BC, de Araujo VE, Godoi IP, de Lemos LL, Godman B, Bennie M, et al. Efficacy of mobile apps to support the care of patients with diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *JMIR Mhealth and Uhealth* 2017;**5**(3):e4.

Cappellini 2007

Cappellini MD, Bejaoui M, Agaoglu L, Porter J, Coates T, Jeng M, et al. Prospective evaluation of patient-reported outcomes during treatment with deferasirox or deferoxamine

for iron overload in patients with beta-thalassemia. *Clinical Therapeutics* 2007;**29**(5):909-17.

Christakis 2004

Christakis NA. Social networks and collateral health effects. *BMJ* 2004;**329**(7459):184-5.

Cobb 1976

Cobb S. Presidential Address-1976. Social support as a moderator of life stress. *Psychosomatic Medicine* 1976;**38**(5):300-14.

Cohen 1985

Cohen S, Wills TA. Stress, social support, and the buffering hypothesis. *Psychological Bulletin* 1985;**98**(2):310-57.

Crosby 2017

Crosby LE, Ware RE, Goldstein A, Walton A, Joffe NE, Vogel, C, et al. Development and evaluation of iManage: a self-management app co-designed by adolescents with sickle cell disease. *Pediatric Blood & Cancer* 2017;**64**(1):139-45.

Czajkowski 2015

Czajkowski SM, Powell LH, Adler N, Naar-King S, Reynolds KD, Hunter CM, et al. From ideas to efficacy: The ORBIT model for developing behavioral treatments for chronic diseases. *Health Psychology* 2015;**34**(10):971-82.

de Jongh 2012

de Jongh T, Gurol-Urganci I, Vodopivec-Jamsek V, Car J, Atun R. Mobile phone messaging for facilitating self-management of long-term illnesses. *Cochrane Database of Systematic Reviews* 2012, Issue 12. [DOI: [10.1002/14651858.CD007459.pub2](https://doi.org/10.1002/14651858.CD007459.pub2)]

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG on behalf of the Cochrane Statistical Methods Group. Chapter 9: Analysing data and undertaking meta-analysis. In: Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

DiMatteo 2002

DiMatteo MR, Giordani PJ, Lepper HS, Croghan TW. Patient adherence and medical treatment outcomes: a meta-analysis. *Medical Care* 2002;**40**(9):794-811.

EPOC 2017

Cochrane Effective Practice, Organisation of Care (EPOC). EPOC Resources for review authors, 2017. What study designs should be included in an EPOC review and what should they be called?. www.epoc.cochrane.org/epoc-resources-review-authors (accessed 15 June 2017).

Evangelini 2010

Evangelini M, Mughal K, Porter JB. Which psychosocial factors are related to chelation adherence in thalassemia? A systematic review. *Hemoglobin* 2010;**34**(3):305-21.

Gurol-Urganci 2013

Gurol-Urganci I, de Jongh T, Vodopivec-Jamsek V, Atun R, Car J. Mobile phone messaging reminders for attendance at healthcare appointments. *Cochrane Database of Systematic Reviews* 2013, Issue 12. [DOI: [10.1002/14651858.CD007458.pub3](https://doi.org/10.1002/14651858.CD007458.pub3)]

Haghpanah 2014

Haghpanah S, Zarei T, Zahedi Z, Karimi M. Compliance and satisfaction with deferasirox (Exjade(R)) compared with deferoxamine in patients with transfusion-dependent beta-thalassemia. *Hematology* 2014;**19**(4):187-91.

Higgins 2011a

Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration 2011. Available from handbook.cochrane.org.

Higgins 2011b

Higgins JPT, Deeks JJ, editor(s). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011c

Higgins JPT, Altman DG, Sterne JAC, editor(s) on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011d

Higgins JPT, Deeks JJ, Altman DG, editor(s) on behalf of the Cochrane Statistical Methods Group. Chapter 16: Special topics in statistics. In: Higgins JPT, Green S, editor(s). *Cochrane Handbook of Systematic Reviews of Interventions*. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgs 2010

Higgs DR, Gibbons RJ. The molecular basis of alpha-thalassemia: a model for understanding human molecular genetics. *Hematology/Oncology Clinics of North America* 2010;**24**(6):1033-54.

Jonassaint 2015

Jonassaint CR, Shah N, Jonassaint J, De Castro L. Usability and feasibility of an mHealth intervention for monitoring and managing pain symptoms in sickle cell disease: the sickle cell disease mobile application to record symptoms via technology (SMART). *Hemoglobin* 2015;**39**(3):162-8.

Koch 1993

Koch DA, Giardina PJ, Ryan M, MacQueen M, Hilgartner MW. Behavioral contracting to improve adherence in patients with thalassemia. *Journal of Pediatric Nursing* 1993;**8**(2):106-11.

Lee 2011

Lee WS, Toh TH, Chai PF, Soo TL. Self-reported level of and factors influencing the compliance to desferrioxamine therapy in multitransfused thalassaemias. *Journal of Paediatrics and Child Health* 2011;**47**(8):535-40.

Lenhart 2015

Lenhart, A. Teens, Social Media & Technology Overview 2015. www.pewinternet.org/2015/04/09/teens-social-media-technology-2015/ (accessed prior to 15 June 2017).

Lin 2014

Lin H, Wu X. Intervention strategies for improving patient adherence to follow-up in the era of mobile information technology: a systematic review and meta-analysis. *PLoS One* 2014;**9**:e104266.

Liu 2014

Liu Q, Abba K, Alejandria MM, Sinclair D, Balanag VM, Lansang MA. Reminder systems to improve patient adherence to tuberculosis clinic appointments for diagnosis and treatment. *Cochrane Database of Systematic Reviews* 2014, Issue 11. [DOI: [10.1002/14651858.CD006594.pub3](https://doi.org/10.1002/14651858.CD006594.pub3)]

Loiselle 2016

Loiselle K, Lee JL, Szulcowski L, Drake S, Crosby LE, Pai AL. Systematic and meta-analytic review: medication adherence among pediatric patients with sickle cell disease. *Journal of Pediatric Psychology* 2016;**41**(4):406-18.

Martin 2013

Martin A, Thompson AA. Thalassaemias. *Pediatric Clinics of North America* 2013;**60**(6):1383-91.

Michie 2013

Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Annals of Behavioral Medicine* 2013;**46**(1):81-95.

Modi 2012

Modi AC, Pai AL, Hommel KA, Hood KK, Cortina S, Hilliard ME, et al. Pediatric self-management: a framework for research, practice, and policy. *Pediatrics* 2012;**129**(2):e473-85.

Pakbaz 2005

Pakbaz Z, Fischer R, Treadwell M, Yamashita R, Fung EB, Calvelli L, et al. A simple model to assess and improve adherence to iron chelation therapy with deferoxamine in patients with thalassaemia. *Annals of the New York Academy of Sciences* 2005;**1054**:486-91.

Payne 2008

Payne KA, Rofail D, Baladi JF, Viala M, Abetz L, Desrosiers MP, et al. Iron chelation therapy: clinical effectiveness, economic burden and quality of life in patients with iron overload. *Advances in Therapy* 2008;**25**(8):725-42.

Pfaeffli 2016

Pfaeffli Dale L, Dobson R, Whittaker R, Maddison R. The effectiveness of mobile-health behaviour change interventions for cardiovascular disease self-management: a systematic review. *European Journal of Preventive Cardiology* 2016;**23**(8):801-17.

Porter 2011

Porter JB, Evangeli M, El-Beshlawy A. Challenges of adherence and persistence with iron chelation therapy. *International Journal of Hematology* 2011;**94**(5):453-60.

Porter 2012

Porter J, Bowden DK, Economou M, Troncy J, Ganser A, Habr D, et al. Health-related quality of life, treatment satisfaction, adherence and persistence in beta-thalassaemia and myelodysplastic syndrome patients with iron overload receiving deferasirox: results from the EPIC clinical trial. *Anemia* 2012;**2012**:297641.

Rachmilewitz 2011

Rachmilewitz EA, Giardina PJ. How I treat thalassaemia. *Blood* 2011;**118**(13):3479-88.

Reeves 2011

Reeves BC, Deeks JJ, Higgins JPT, Wells GA on behalf of the Cochrane Non-Randomised Studies Methods Group. Chapter 13: Including non-randomized studies. In: Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rund 2005

Rund D, Rachmilewitz E. Beta-thalassaemia. *New England Journal of Medicine*. 2005;**353**(11):1135-46.

Sabate 2003

Sabate E. Adherence to long-term therapies: evidence for action. www.who.int/chp/knowledge/publications/adherence_report/en/ (accessed prior to 15 June 2017).

Schünemann 2011a

Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH on behalf of the Cochrane Applicability and Recommendations Methods Group and the Cochrane Statistical Methods Group. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Shah 2014

Shah N, Jonassaint J, De Castro L. Patients welcome the Sickle Cell Disease Mobile Application to Record Symptoms via Technology (SMART). *Hemoglobin* 2014;**38**(2):99-103.

Smith 2015a

Smith A. U.S. smartphone use in 2015. www.pewinternet.org/2015/04/01/us-smartphone-use-in-2015/ (accessed prior to 15 June 2017).

Smith 2015b

Smith C, Gold J, Ngo TD, Sumpter C, Free C. Mobile phone-based interventions for improving contraception use. *Cochrane Database of Systematic Reviews* 2015, Issue 6. [DOI: [10.1002/14651858.CD011159.pub2](https://doi.org/10.1002/14651858.CD011159.pub2)]

Sterne 2011

Sterne JAC, Egger M, Moher D, editor(s) on behalf of the Cochrane Bias Methods Group. Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Sterne 2016

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;**355**:i4919.

Taher 2010

Taher A, Al Jefri A, Elalfy MS, Al Zir K, Daar S, Rofail D, et al. Improved treatment satisfaction and convenience with deferasirox in iron-overloaded patients with beta-thalassemia: results from the ESCALATOR trial. *Acta Haematologica* 2010;**123**(4):220-5.

Thakkar 2016

Thakkar J, Kurup R, Laba TL, Santo K, Thiagalingam A, Rodgers A, et al. Mobile telephone text messaging for medication adherence in chronic disease: a meta-analysis. *JAMA Internal Medicine* 2016;**176**(3):340-9.

Trachtenberg 2011

Trachtenberg F, Vichinsky E, Haines D, Pakbaz Z, Mednick L, Sobota A, et al. Iron chelation adherence to deferoxamine and deferasirox in thalassemia. *American Journal of Hematology* 2011;**86**(5):433-6.

Trachtenberg 2012a

Trachtenberg FL, Mednick L, Kwiatkowski JL, Neufeld EJ, Haines D, Pakbaz Z, et al. Beliefs about chelation among thalassemia patients. *Health and Quality of Life Outcomes* 2012;**10**:148.

Trachtenberg 2014

Trachtenberg FL, Gerstenberger E, Xu Y, Mednick L, Sobota A, Ware H, et al. Relationship among chelator adherence, change in chelators, and quality of life in thalassemia. *Quality of Life Research* 2014;**23**(8):2277-88.

Treadwell 2001

Treadwell MJ, Weissman L. Improving adherence with deferoxamine regimens for patients receiving chronic transfusion therapy. *Seminars in Hematology* 2001;**38**(1 Suppl 1):77-84.

Vekeman 2016

Vekeman F, Sasane M, Cheng WY, Ramanakumar AV, Fortier J, Qiu Y, et al. Adherence to iron chelation therapy and associated healthcare resource utilization and costs in Medicaid patients with sickle cell disease and thalassemia. *Journal of Medical Economics* 2016;**19**(3):292-303.

Walsh 2014

Walsh KE, Cutrona SL, Kavanagh PL, Crosby LE, Malone C, Lobner K, et al. Medication adherence among pediatric patients with sickle cell disease: a systematic review. *Pediatrics* 2014;**134**(6):1175-83.

Ware 2013

Ware HM, Kwiatkowski JL. Evaluation and treatment of transfusional iron overload in children. *Pediatric Clinics of North America* 2013;**60**(6):1393-406.

Weatherall 2012

Weatherall DJ. The definition and epidemiology of non-transfusion-dependent thalassemia. *Blood Reviews* 2012;**26** Suppl 1:S3-6.

Whitehead 2016

Whitehead L, Seaton P. The effectiveness of self-management mobile phone and tablet apps in long-term condition management: a systematic review. *Journal of Medical Internet Research* 2016;**18**(5):e97.

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abu Samra 2015	No technology intervention
Antoniou 2015	Physician-centered technology intervention
Arbaiy 2017	Physician-centered technology intervention

Study	Reason for exclusion
Bal 2014	Not an original clinical research study
Bobati 2016	Not an original clinical research study
Deftereos 2001	Physician-centered technology intervention
Dehkordi 2008	No technology intervention
Gambari 2007	No technology intervention
Jonassaint 2012	Not an original clinical research study
Lederer 2009	Physician-centered technology intervention
Leonard 2017	Uncontrolled pilot before after study
Nawaz 2012	Not an original clinical research study
Olivieri 1991	No technology intervention
Paholpak 2006	No technology intervention
Paokanta 2014	Not an original clinical research study
Piga 2013	Physician-centered technology intervention
Santini 2017	Physician-centered technology intervention
Trachtenberg 2012b	No technology intervention
Ward 2016	Intervention development and usability pilot study
Yamashita 1998	Not an original clinical research study

Characteristics of ongoing studies *[ordered by study ID]*

IRCT20170826035907N1

Trial name or title	The effect of self-caring using Tele-Nursing on thalassemia teenagers self-efficacy
Methods	Randomized ("simple randomization") Parallel design Not blinded
Participants	Beta thalassemia in adolescents Age: 13 - 18 years Gender: both Inclusion criteria: indices for entering and exiting research include: tending to participate in the study and telephone teaching; having active file records in thalassemia section of the hospital; lack of serious disorder in parents and another family members; having cell phone personally or in family or having ability for installing Telegram application; lack of behavioral, mental, hearing and

IRCT20170826035907N1 (Continued)

	speech disorders according to the medical records and lack of another same as diabetic and cardiac disease; teenager disease lasting more than a year
Interventions	Intervention group: self-caring teaching using tele-nursing through telegram in form of contacting 6 telegram call during 8 weeks Control group: just routine teaching were received
Outcomes	Primary outcomes: efficacy Timepoints: before intervention, 3 months after the intervention. Method of measurement: children and teenagers Self-efficacy Scale (SEQ-C)
Starting date	23 September 2009
Contact information	Fatemeh Alaei Kerafroudi. Email: Falaee@iautmu.ac.ir. Telephone: +98 21 2200 6660. Address: Islamic Azad University, Tehran Medical Sciences Branch, Khaghani St, Shariati St, Tehran 1916893813, Tehran, Iran (Islamic Republic of)
Notes	Sources of monetary support: Islamic Azad University

IRCT20180207038655N1

Trial name or title	The Effect of Mobile Phone-Based Education on Patients with Thalassemia
Methods	RCT ("toss and coin") Parallel design Not blinded Inclusion criteria: 20 - 30 years of age; have a mobile phone; depends on the blood transfusion twice a month; having at least reading and writing skills; ability to use telegram software Exclusion criteria: disabling disorders unrelated to thalassemia
Participants	"Patients with 20-30 years old" (but also states: "Age minimum: no limit; Age maximum: no limit") Gender: both Inclusion criteria: having a mobile; depending on the blood transfusion twice a month; having at least reading and writing skills; ability to use telegram software Exclusion criteria: disabling disorders unrelated to thalassemia
Interventions	Intervention group: every week 4 messages are received in relation to the improvement of stress, anxiety, depression and pain for 3 months Control group: only receive routine care
Outcomes	Primary outcomes: anxiety; depression; pain; stress Time points: beginning and the end of intervention Method of measurement: questionnaire Secondary outcomes: score of life quality Timepoint: 3 months after study. Method of measurement: questionnaire

IRCT20180207038655N1 (Continued)

Starting date	11 March 2018
Contact information	Mahsa Imanian. Email: M.Imanian@jums.ac.ir. Telephone: +98 71 5423 5521. Address: Janbazan 7417978647 Jahrom, Iran (Islamic Republic of)
Notes	Sources of monetary support: Jahrom University of Medical Sciences

RCT: randomized controlled trial

APPENDICES
Appendix 1. Search Methods - Electronic Searching

Database/ Resource	Strategy
CENTRAL, DARE and HTA Databases (via the Cochrane Library, all years)	#1 MeSH descriptor: [Thalassemia] explode all trees
	#2 Thalass* <i>mia</i> *
	#3 alpha-thal*
	#4 beta-thal*
	#5 delta-thal*
	#6 #1 or #2 or #3 or #4 or #5
	#7 MeSH descriptor: [Cell Phones] explode all trees
	#8 (Cellphone* or ((cell* or mobile) and (Phone* or telephone*)) or iphone*)
	#9 MeSH descriptor: [Microcomputers] explode all trees
	#10 MeSH descriptor: [Mobile Applications] this term only
	#11 (Microcomputer* or ipad* or pda* or personal digital assistant* or blackberry* or android* or smartphone* or smart phone* or tablet or app or apps)
	#12 ((mobile or electronic* or handheld or hand-held) and (application* or communication* or technolog* or game* or tool* or device* or monitor* or mentor* or computer*))
	#13 MeSH descriptor: [Internet] explode all trees
	#14 MeSH descriptor: [Computer Simulation] this term only
	#15 MeSH descriptor: [Electronic Mail] this term only
	#16 MeSH descriptor: [Reminder Systems] this term only
	#17 MeSH descriptor: [Wireless Technology] this term only
	#18 MeSH descriptor: [Software] explode all trees
	#19 (internet OR computer simulation OR email* OR e-mail* OR electronic mail OR remind* system* OR software OR Bluetooth OR web-based)
	#20 (wireless AND (technolog* OR communicat*))
	#21 MeSH descriptor: [Video Recording] this term only

(Continued)

#22 MeSH descriptor: [Videoconferencing] explode all trees

#23 MeSH descriptor: [Telemedicine] explode all trees

#24 MeSH descriptor: [Text Messaging] this term only

#25 (video recording* or videoconference* or teleconference* or texting or texts or text message* or SMS or short messag* service)

#26 (mobile health or mhealth or ehealth or m-health or e-health or mcare or electronic health or e-monitoring or telehealth* or telemonitoring or telementoring or telecare or telemedicine or telecommunication*)

#27 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26

#28 #6 and #27

PubMed

(Thalassemia[tw] OR Thalassemias[tw] or α -thalassemia[tw] OR α -thalassemias[tw] OR α -thal[tw] or alpha-thalassemia[tw] OR alpha-thalassemias[tw] OR β -thalassemia[tw] OR β -thalassemias[tw] OR β -thal[tw] OR beta-thalassemia[tw] OR beta-thalassemias[tw] OR δ -thalassemia[tw] OR δ -thalassemias[tw] OR δ -thal[tw] OR delta-thalassemia[tw] OR delta-thalassemias[tw] OR Thalassaemia[tw] OR Thalassaemias[tw] or α -thalassaemia[tw] OR α -thalassaemias[tw] OR α -thal[tw] or alpha-thalassaemia[tw] OR alpha-thalassaemias[tw] OR β -thalassaemia[tw] OR β -thalassaemias[tw] OR β -thal[tw] OR beta-thalassaemia[tw] OR beta-thalassaemias[tw] OR δ -thalassaemia[tw] OR δ -thalassaemias[tw] OR δ -thal[tw] OR delta-thalassaemia[tw] OR delta-thalassaemias[tw])

AND ("mobile health"[tw] OR "mhealth"[tw] OR "ehealth"[tw] OR "m-health"[tw] OR "e-health"[tw] OR "mcare"[tw] OR "cellphone"[tw] OR "cellphones"[tw] OR "cell phones"[tw] OR "cell phone" OR "cellular phone"[tw] OR "cellular phones"[tw] OR "cellular telephone"[tw] OR "cellular telephones"[tw] OR "mobile phone"[tw] OR "mobile phones"[tw] OR "mobile telephone"[tw] OR "mobile telephones"[tw] OR "iphone"[tw] OR "iphones"[tw] OR "microcomputer"[tw] OR "microcomputers"[tw] OR "handheld computer"[tw] OR "handheld computers"[tw] OR "hand held computer"[tw] OR "hand held computers"[tw] OR "ipad"[tw] OR "ipads"[tw] OR "pda"[tw] OR "pdas"[tw] OR "personal digital assistant"[tw] OR "personal digital assistants"[tw] OR "blackberry"[tw] OR "android"[tw] OR "androids"[tw] OR "smartphone"[tw] OR "smartphones"[tw] OR "smart phone"[tw] OR "smart phones"[tw] OR "tablet"[tw] OR "apps"[tw] OR "app"[tw] OR "mobile application"[tw] OR "mobile applications"[tw] OR "mobile communication"[tw] OR "mobile communications"[tw] OR "mobile technology"[tw] OR "mobile technologies"[tw] OR "mobile game"[tw] OR "mobile games"[tw] OR "internet"[tw] OR "computer simulation"[tw] OR "email"[tw] OR "emails"[tw] OR "emailing"[tw] OR "e-mail"[tw] OR "e-mails"[tw] OR "e-mailing"[tw] OR "electronic mail"[tw] OR "reminder systems"[tw] OR "reminder system"[tw] OR "wireless technology"[tw] OR "wireless technologies"[tw] OR "wireless communication"[tw] OR "wireless communications"[tw] OR "software"[tw] OR "video recording"[tw] OR "video recordings"[tw] OR teleconference*[tw] OR "text message"[tw] OR "text messaging"[tw] OR "texting"[tw] OR "text"[tw] OR "texts"[tw] OR "SMS"[tw] OR "short message service"[tw] OR "text messages"[tw] OR "Handheld device"[tw] OR "handheld devices"[tw] OR "mobile tool"[tw] OR "mobile tools"[tw] OR "electronic device"[tw] OR "electronic devices"[tw] OR "electronic tool"[tw] OR "electronic tools"[tw] OR "electronic health"[tw] OR "electronic monitoring"[tw] OR "e-monitoring"[tw] OR "electronically monitor"[tw] OR "electronic mentoring"[tw] OR "telehealth"[tw] OR "telehealthcare"[tw] OR "telemonitoring"[tw] OR "telementoring"[tw] OR "telecare"[tw] OR "telemedicine"[tw] OR "telecommunication"[tw] OR "telecommunications"[tw] OR "videoconferencing"[tw] OR "videoconference"[tw] OR "bluetooth"[tw] OR "web-based"[tw])

MEDLINE (OvidSP, 1946 to present)

1. exp Thalassemia/
2. Thalass?emia*.af.
3. alpha-thal*.af.
4. beta-thal*.af.
5. delta-thal*.af.

(Continued)

6. 1 or 2 or 3 or 4 or 5
7. exp Cell Phones/
8. (Cellphone* or ((cell* or mobile) and (Phone* or telephone*)) or iphone*).af.
9. exp Microcomputers/
10. Mobile Applications/
11. (Microcomputer* or ipad* or pda* or personal digital assistant* or blackberry* or android* or smartphone* or smart phone* or tablet or app or apps).af.
12. ((mobile or electronic* or handheld or hand-held) and (application* or communication* or technolog* or game* or tool* or device* or monitor* or mentor* or computer*)).af.
13. exp Internet/
14. Computer Simulation/
15. Electronic mail/
16. Reminder Systems/
17. Wireless Technology/
18. exp Software/
19. (internet OR computer simulation OR email* OR e-mail* OR electronic mail OR remind* system* OR software OR Bluetooth OR web-based).af.
20. (wireless AND (technolog* OR communicat*)).af.
21. Video Recording/
22. exp Videoconferencing/
23. exp Telemedicine/
24. Text Messaging/
25. (video recording* or videoconference* or teleconference* or texting or texts or text message* or SMS or short messag* service).af.
26. (mobile health or mhealth or ehealth or m-health or e-health or mcare or electronic health or e-monitoring or telehealth* or telemonitoring or telementoring or telecare or telemedicine or telecommunication*).af.
27. or/7-26
28. 6 and 27

Embase (OvidSP, 1974 to present)

1. exp Thalassemia/
2. Thalass?emia*.af.
3. alpha-thal*.af.
4. beta-thal*.af.
5. delta-thal*.af.
6. 1 or 2 or 3 or 4 or 5
7. exp Mobile Phone/
8. (Cellphone* or ((cell* or mobile) and (Phone* or telephone*)) or iphone*).af.

(Continued)

9. Microcomputer/
10. Mobile Application/
11. (Microcomputer* or ipad* or pda* or personal digital assistant* or blackberry* or android* or smartphone* or smart phone* or tablet or app or apps).af.
12. ((mobile or electronic* or handheld or hand-held) and (application* or communication* or technolog* or game* or tool* or device* or monitor* or mentor* or computer*)).af.
13. Internet/
14. Computer Simulation/
15. E-mail/
16. Reminder System/
17. Wireless Communication/
18. Software/
19. (internet OR computer simulation OR email* OR e-mail* OR electronic mail OR remind* system* OR software OR Bluetooth OR web-based).af.
20. (wireless AND (technolog* OR communicat*)).af.
21. Videorecording/
22. Videoconferencing/
23. exp Telemedicine/
24. Text Messaging/
25. (video recording* or videoconference* or teleconference* or texting or texts or text message* or SMS or short messag* service).af.
26. (mobile health or mhealth or ehealth or m-health or e-health or mcare or electronic health or e-monitoring or telehealth* or telemonitoring or telementoring or telecare or telemedicine or telecommunication*).af.
27. or/7-26
28. 6 and 27

CINAHL (EBSCOHost, 1937 to present)

- S1 MH thalassemia
- S2 TX thalass#emia*
- S3 TX alpha-thal*
- S4 TX beta-thal*
- S5 TX delta-thal*
- S6 S1 OR S2 OR S3 OR S4 OR S5
- S7 (MH "Cellular Phone") OR (MH "Smartphone")
- S8 TX Cellphone* or ((cell* or mobile) and (Phone* or telephone*)) or iphone*
- S9 (MH "Microcomputers") OR (MH "Computers, Portable+")
- S10 (MH "Mobile Applications")

(Continued)

- S11 TX Microcomputer* or ipad* or pda* or personal digital assistant* or blackberry* or android* or smartphone* or smart phone* or tablet or app or apps
- S12 TX (mobile or electronic* or handheld or hand-held) and (application* or communication* or technolog* or game* or tool* or device* or monitor* or mentor* or computer*)
- S13 (MH "Internet")
- S14 (MH "Computer Simulation")
- S15 (MH "Electronic Mail")
- S16 (MH "Reminder Systems")
- S17 (MH "Wireless Communications")
- S18 (MH "Software") OR (MH "Communications Software")
- S19 TX internet OR computer simulation OR email* OR e-mail* OR electronic mail OR remind* system* OR software OR Bluetooth OR web-based
- S20 TX wireless AND (technolog* OR communicat*)
- S21 (MH "Videorecording") OR (MH "Videoconferencing+")
- S22 (MH "Telecommunications+") OR (MH "Telehealth+")
- S23 TX video recording* or videoconference* or teleconference* or texting or texts or text message* or SMS or short messag* service
- S24 TX mobile health or mhealth or ehealth or m-health or e-health or mcare or electronic health or e-monitoring or telehealth* or telemonitoring or telementoring or telecare or telemedicine or telecommunication*
- S25 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24
- S26 S6 AND S25

PsycInfo (EBSCOHost, 1900 to present)

- S1 TX thalass#emia*
- S2 TX alpha-thal*
- S3 TX beta-thal*
- S4 TX delta-thal*
- S5 S1 OR S2 OR S3 OR S4
- S6 DE "Mobile Devices" OR DE "Cellular Phones" OR DE "Electronic Communication" OR DE "Blog" OR DE "Computer Mediated Communication" OR DE "Electronic Learning" OR DE "Social Media" OR DE "Text Messaging"
- S7 TX Cellphone* or ((cell* or mobile) and (Phone* or telephone*)) or iphone*
- S8 DE "Microcomputers"
- S9 TX Microcomputer* or ipad* or pda* or personal digital assistant* or blackberry* or android* or smartphone* or smart phone* or tablet or app or apps
- S10 TX (mobile or electronic* or handheld or hand-held) and (application* or communication* or technolog* or game* or tool* or device* or monitor* or mentor* or computer*)
- S11 DE "Internet"
- S12 DE "Computer Simulation"

(Continued)

S13 DE "Computer Software" OR DE "Groupware"

S14 TX internet OR computer simulation OR email* OR e-mail* OR electronic mail OR remind* system* OR software OR Bluetooth OR web-based

S15 TX wireless AND (technolog* OR communicat*)

S16 DE "Teleconferencing" OR DE "Telemedicine"

S17 TX video recording* or videoconference* or teleconference* or texting or texts or text message* or SMS or short messag* service

S18 TX mobile health or mhealth or ehealth or m-health or e-health or mcare or electronic health or e-monitoring or telehealth* or telemonitoring or telementoring or telecare or telemedicine or telecommunication*

S19 S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18

S20 S5 AND S19

Web of Science & Social Sciences Conference Proceedings Indexes (CPSI-S & CPSSI, 1990 to current)

#1 TOPIC: (Thalass*emia*)

#2 TOPIC: (alpha-thal*)

#3 TOPIC: (beta-thal*)

#4 TOPIC: (delta-thal*)

#5 #4 OR #3 OR #2 OR #1

#6 TOPIC: (Cellphone* or ((cell* or mobile) and (Phone* or telephone**)) or iphone*)

#7 TOPIC: (Microcomputer* or ipad* or pda* or personal digital assistant* or blackberry* or android* or smartphone* or smart phone* or tablet or app or apps)

#8 TOPIC: ((mobile or electronic* or handheld or hand-held) and (application* or communication* or technolog* or game* or tool* or device* or monitor* or mentor* or computer*))

#9 TOPIC: (internet OR computer simulation OR email* OR e-mail* OR electronic mail OR remind* system* OR software OR Bluetooth OR web-based)

#10 TOPIC: (wireless AND (technolog* OR communicat*))

#11 TOPIC: (video recording* or videoconference* or teleconference* or texting or texts or text message* or SMS or short messag* service)

#12 TOPIC: (mobile health or mhealth or ehealth or m-health or e-health or mcare or electronic health or e-monitoring or telehealth* or telemonitoring or telementoring or telecare or telemedicine or telecommunication*)

#13 #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6

#14 #13 AND #5

Institute of Electrical and Electronics Engineers Explore (IEEE Xplore, 1963 to present)

thalassemia OR thalassemia

ISRCTN registry

thalassemia OR thalassaemia

ClinicalTrials.gov [new search interface]

Condition/ Disease: thalassemia

Other terms: phone OR smartphone OR computer OR mobile OR electronic OR app OR game OR wireless OR email OR video OR text OR sms OR video OR electronic OR internet OR web OR device

(Continued)

OR technology OR Bluetooth OR online OR remote OR monitor OR communication OR telecommunication OR teleconference OR videoconference OR videoconferencing OR teleconference OR teleconferencing

WHO International Clinical Trials Registry Platform (ICTRP)

[Advanced Search Form]

Condition: thalassemia OR thalassaemia

Intervention: phone OR smartphone OR computer OR mobile OR electronic OR app OR game OR wireless OR email OR video OR text OR sms OR video OR electronic OR internet OR web OR device OR technology OR Bluetooth OR online OR remote OR monitor OR communication OR telecommunication OR teleconference OR videoconferenc* OR teleconference*

Recruitment Status: All

CONTRIBUTIONS OF AUTHORS

Sherif Badawy: conceiving the review, selection of trials, eligibility assessment, risk of bias assessment, data extraction, development of review content, methodological expert, and content expert.

Kerry Morrone: selection of trials, eligibility assessment, risk of bias assessment, data extraction, development of review content, and content expert.

Alexis Thompson: development of review content and content expert.

Tonya Palermo: eligibility assessment, risk of bias assessment, development of review content, and methodological expert.

DECLARATIONS OF INTEREST

All authors: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have removed "uncontrolled pilot before after studies" from the inclusion criteria, as this is not an appropriate study design to be included and does not accurately reflect the content of the EPOC guidelines that we have referenced, which strongly discourages the inclusion of uncontrolled before-and-after studies ([EPOC 2017](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

*Cell Phone; *Chelation Therapy; *Medication Adherence; *Therapy, Computer-Assisted; Age Factors; Disease Management; Iron Overload [*drug therapy]; Thalassemia [*therapy]

MeSH check words

Adolescent; Adult; Child; Humans