Journal Pre-proof

Can eHealth applications improve renal transplant outcomes for adolescents and young adults?

Kim C.M. Bul, Christopher Bannon, Nithya Krishnan, Amber Dunlop, Ala Szczepura

PII: S0955-470X(23)00014-9

DOI: https://doi.org/10.1016/j.trre.2023.100760

Reference: YTRRE 100760

To appear in: *Transplantation Reviews*

Please cite this article as: K.C.M. Bul, C. Bannon, N. Krishnan, et al., Can eHealth applications improve renal transplant outcomes for adolescents and young adults?, *Transplantation Reviews* (2023), https://doi.org/10.1016/j.trre.2023.100760

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2023 Published by Elsevier Inc.

Journal Pre-proof

Title: Can eHealth applications improve renal transplant outcomes for adolescents and young adults?

Subtitle: A systematic review

Dr. Kim CM Bul[1], Dr. Christopher Bannon[2], Prof. Nithya Krishnan[3], Ms. Amber Dunlop[4], Prof. Ala Szczepura[5]

[1]Coventry University, Institute for Health and Wellbeing, Centre of Intelligent Healthcare, West Midlands, Coventry, United Kingdom

[2]Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom

[3]University Hospital Coventry and Warwickshire NHS Trust, Renal, West Midlands, Coventry, United Kingdom

[4]University Hospital Coventry and Warwickshire NHS Trust, Library & Knowledge Services, West Midlands, Coventry, United Kingdom

[5] Coventry University, Institute for Health and Wellbeing, Centre for Healthcare Research, West Midlands, Coventry, United Kingdom

Corresponding Author

Kim CM Bul, MSc, PhD

Coventry University

Richard Crossman building (4th floor)

Jordan Well

CV1 5RW, Coventry

West Midlands

United Kingdom

Journal Pre-proof

Email address: kim.bul@coventry.ac.uk

Telephone number: 07392096816

Word count abstract: 203

Word count for text (excl. references): 2968

Number of figures and tables: 5

Journal Pre-proof

Abstract

Background and Objectives: Adherence to medical treatment following a kidney transplant is particularly challenging during adolescence and young adulthood.

There is increasing evidence of the benefits of the use of computer and mobile technology (labelled as eHealth hereafter) including serious gaming and gamification in many clinical areas. We aimed to conduct a systematic review of such interventions designed to improve self-management skills, treatment adherence and clinical outcomes in young kidney transplant recipients aged 16 to 30 years.

Method: The Cochrane Library, MEDLINE, EMBASE, PsycINFO, SCOPUS and CINAHL databases were searched for studies published between 01 January 1990 and 20 October 2020. Articles were short-listed by two independent reviewers based on pre-defined inclusion/exclusion criteria. Reference lists were screened and authors of published conference abstracts contacted. Two reviewers independently appraised selected articles, systematically extracted data and assessed the quality of individual studies (CASP and SORT). Thematic analysis was used for evidence synthesis; quantitative meta-analysis was not possible.

Results: A total of 1,098 unique records were identified. Short-listing identified four eligible studies, all randomized controlled trials (*n*=266 participants). Trials mainly focused on mHealth applications or electronic pill dispensers (mostly for patients >18 years old). Most studies reported on clinical outcome measures. All showed improved adherence but there were no differences in the number of rejections. Study quality was low for all four studies.

Conclusions: The findings of this review suggest that eHealth interventions can improve treatment adherence and clinical outcomes for young kidney transplant patients. More robust and high-quality studies are now needed to validate these findings. Future studies

Journal Pre-proof

should also extend beyond short-term outcomes, and consider cost of implementation. The review was registered with PROSPERO (CRD42017062469).

Keywords: Systematic Review, eHealth, Adolescent, Young adult, Renal transplant outcomes

Journal Pre-proof

1. Introduction

Long-term kidney functioning post transplantation requires patients to self-manage their immunosuppressive medication and hospital consultations. Young kidney transplant recipients are particularly at high risk for poor treatment adherence to immunosuppressive medication and present poorer clinical outcomes in terms of long-term graft survival rates (Prendergast & Gaston, 2010; Rianthavorn & Ettenger, 2005). Dobbels and colleagues (2010) report nonadherence ranges from 22.4% to 43.2% across pediatric and adolescent renal patients. Reasons for non-adherence remain speculative but are possibly related to adolescents' immature decision-making and need to explore boundaries, affecting their self-management abilities (Prendergast & Gaston, 2010; Zhu et al., 2017). This presents daily challenges for their surrounding family members and health care professionals (Nguyen et al., 2020). Interventions supporting self-management and treatment adherence are therefore needed to support young adults receiving kidney transplants.

Even many older patients fail to adhere to their treatment regime with non-adherence ranging from 15% to 40% (Duncan et al., 2017). This variation is caused by a lot of 'unknowns' regarding the methodologies of how to measure and define adherence (Osterberg & Blaschke, 2005). Adherence has previously been defined in the context of the medical model referring to being compliant with recommended medical instructions but this does not reflect its multifactorial nature and the patient as an equal partner in decision-making. Therefore, within the current review we focus on adherence as "the extent to which a person's behaviour, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (Sabaté & World Health Organization, 2003; Subho Chakrabarti, 2014). Reasons include medication side-effects such as changed body appearance and appetite (Moons et al., 2003; Rovelli et al., 1989; Sketris et al., 1994), forgetting a dose as well as treatment duration and complexity

(Osterberg & Blaschke, 2005). This leads to severe consequences such as late acute rejection in up to 60% of patients and a long term graft survival of only 30-35% (Zhu et al., 2017). Rejection post transplantation leads to morbidity and potential mortality, alongside impaired quality of life (QoL) and substantial economic costs (Prendergast & Gaston, 2010).

Evidence regarding treatment effectiveness on improved treatment adherence and clinical outcomes are mixed (Nguyen et al., 2020). A Cochrane systematic review (2008) with 83 interventions demonstrated that less than 50% are effective on the long-term in terms of treatment adherence whereas only 25 interventions demonstrated improvements on at least one clinical outcome (Haynes et al., 2008). Effective interventions were complex and only demonstrated small to medium effect sizes (Haynes et al., 2008). Limited effectiveness of adherence interventions in solid organ transplant patients (with broad age range) was also demonstrated by another systematic literature review (2007) which included face-to-face as well as technology-based interventions (Duncan et al., 2017; Nerini, Bruno, Citterio, & Schena, 2016; De Bleser, Matteson, Dobbels, Russell, & De Geest, 2009).

A more recent meta-analysis and systematic review however, demonstrated that interventions focussed on improving treatment adherence for immunosuppressive medications in kidney transplant patients are effective (Zhu et al., 2017). Adherence interventions delivered through a pharmacist, intervention groups and continuing education were more effective than no intervention. Most interventions appear to be multicomponent and health care professionals perceive it as most effective to educate patients on how to take their medication while they are recovering in the hospital (Nguyen et al., 2020). De Bleser and colleagues (2009) included one high-quality randomized controlled trial with the intervention group (consisting of a home visit and three follow-up phone interviews) having the greatest decrease in non-adherence across nonadherent kidney transplant patients. However, control and intervention groups both had the same level of nonadherence at 6

months follow-up suggesting that participating in the study improved overall adherence rates. These systematic overviews lack specific information concerning the age group 16 to 30 who are seen as a high-risk group in terms of treatment adherence and clinical outcomes. Indeed, a pervious review by Dobbels and colleagues (2010) indicates that research focussing on improving medication adherence in young transplant populations is lacking in terms of quantity and quality. Given that most adolescents own smartphones nowadays and are familiar and intrinsically engaged with technology (Browning et al., 2016), an increasing amount of research is focussing on developing eHealth interventions in this new era including serious games and gamification to improve knowledge, self-management and treatment adherence in patients with chronic conditions (Charlier et al., 2016). Mobile phones are promoted as an education and behavioural cue tool to remind young kidney transplant patients to take their medication (Fredericks & Dore-Stites, 2010). Dashboards for pharmacists have been developed to monitor medication safety across kidney transplant recipients with some preliminary validation (Taber et al., 2019). Also, electronic pillboxes in combination with other intervention components are developed, but not scientifically evaluated, to improve immunosuppressant treatment adherence in kidney transplant patients aged from 11 to 24 years (the TAKE-IT Study Group et al., 2014).

More recent studies describe online platform usage focussed on improving self-management skills in adolescent solid organ transplant patients through education and video-based peer interaction (Korus et al., 2015; Shellmer et al., 2011, 2016). However, it seems important to focus on kidney transplant patients in specific as they have different outcome patterns in terms of one-year survival rate (98% versus 80-89%) and health-related QoL compared to other organ recipients (Pinson et al., 2000). This implies there are different needs for this subgroup of solid organ transplant recipients and therefore important implications for intervention focus.

Journal Pre-proof

The current systematic review addresses how effective eHealth applications are in improving renal transplant outcomes across adolescents and young adults compared to a control condition or within a pre-post-test design after receiving their transplant. It aims to identify and appraise the existing evidence of eHealth interventions (including serious gaming and gamification) in improving self-management primarily, and treatment adherence as well as clinical outcomes among kidney transplant recipients aged 16-30 years. This will provide an improved understanding about which eHealth interventions contribute to improved outcomes in this vulnerable group of patients.

2. Materials and Methods

The review protocol was registered in PROSPERO prospectively on 10th of April 2017 and can be found through ID number CRD42017062469 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017062469). The PRISMA 2020 statement was followed to comply with reporting guidelines for systematic reviews (see Supplemental File 1).

2.1 Inclusion and exclusion criteria

Studies were included if published in English after 1990 and contained ICT interventions (delivered through any device) fully or partly focussed on young kidney transplant patients (aged 16 to 30 years) and/or their family members. Treatment adherence outcome measures are clinical, psychological, resource use and intervention user views focussed. Non-primary research and articles with interventions focussing on health care professionals and donors were excluded. There were no limits on the type of study design.

Journal Pre-proof

2.2 Information sources

A common search strategy was defined in MEDLINE (see Supplemental File 2) and used across EMBASE, PsychINFO, SCOPUS, CINAHL and The Cochrane Library. Reference lists of eligible and excluded non-primary studies were screened manually to identify further studies. Study authors were contacted to provide further information on studies in preparation. Initial searches were performed by the Library & Knowledge Services of UHCW on 17th of January 2018 and were updated by them on 20th of October 2020.

2.3 Search strategies, study selection and data extraction

The search terms used in the review are: transplant recipient, kidney transplant, medication adherence, self-management, internet, video games, mobile applications, computers and smartphones (see Supplemental File 2). Abstracts were short-listed independently by two authors (KB, CB), compared by a third (AS) and any disagreements resolved through discussion. A standardized data extraction sheet was used on which one author (KB) extracted data from included studies and a second author (CB) reviewed this, with any disagreements resolved through discussion.

2.4 Quality Appraisal of individual studies

Quality assessment of RCTs was performed using the Critical Appraisal Skills Programme (CASP) checklist (Brice, n.d.) independently by two reviewers (KB, CB) followed by discussion and final agreement between them. Level of evidence for each individual study was elaborated with a GRADE approach, using the Strength of Recommendation Taxonomy (SORT, Ebell et al., 2004). This consists of Level 1 (good quality), Level 2 (limited quality) and Level 3 (other evidence).

Journal Pre-proof

2.5 Summary measures

Where possible, results of individual RCTs were recorded as mean differences for continuous variables and odds ratios for dichotomous variables with 95% confidence intervals (CIs) to indicate intervention effectiveness against a control group. For pre- and post-test measurements, effect sizes were reported and if not available calculated through Cohen's *d* (Cohen, 1988). Given the heterogeneity of studies, no meta-analyses or subgroup analyses could be conducted. Instead a narrative synthesis, using thematic analyses to cluster study results in (sub)themes, was undertaken to report outcome measures (Popay et al., 2006).

3 Results

3.1 Study selection

After duplicate removal, electronic database searches resulted in 673 unique records. Screening title and abstract resulted in excluding 670 articles, including three relevant abstracts (Han et al., 2016; Sinnya et al., 2015)(Wüthrich et al., 2012) for which no full-text could be retrieved. One study author was contacted on 19th of November 2018 to confirm that only a poster abstract was available and no further research was published (Han et al., 2016). Based on the other two abstracts (Sinnya et al., 2015; Wüthrich et al., 2012), no further research could be retrieved based on their publication pages. From the three included full-text article reads one article (Henriksson et al., 2016) met the inclusion criteria. Reference lists of the included study and excluded non-primary research were screened to see if any additional references were missed, resulting in three other relevant articles (McGillicuddy et al., 2013; Reese et al., 2017; Schmid et al., 2017). Therefore, a total of four articles was included (see Figure 1).

(Insert Figure 1 black/white here)

Journal Pre-proof

3.2 Study characteristics

3.2.1 Design

Included European (Sweden, Germany; *n*=2) and American (*n*=2) RCT studies consist of two prospective trials (Henriksson et al., 2016; Schmid et al., 2017), and one proof-of-concept trial (McGillicuddy et al., 2013). Participants were randomly allocated to one (or two) intervention groups and standard care, expect for one study where participants were offered a wireless pill bottle (excluding reminders and notifications) to track adherence (Reese et al., 2017). Standard care included immunosuppressive regime (twice a day) (Henriksson et al., 2016) and clinic visits every 4 to 6 weeks depending on the medical indication and time since transplantation (McGillicuddy et al., 2013; Schmid et al., 2017). It also includes educational materials and availability of health care professionals (McGillicuddy et al., 2013; Schmid et al., 2017). Standard care was not described by one study (Henriksson et al., 2016). Other study characteristics are described into more detail in Table 1.

(Insert Table 1 here)

3.2.2 Intervention description

Telemedicine to support case management (Schmid et al., 2017) and electronic / wireless drug dispensers or medication trays (Henriksson et al., 2016; McGillicuddy et al., 2013; Reese et al., 2017) were used to improve kidney transplant outcomes. Core features of telemedically supported case management are remote telemonitoring and real-time video consultations with case management services, medical consultation/instructions, self-care-related education, extra self-management support and coaching in health-specific issues (Schmid et al., 2017). The prototype mHealth intervention, which consists of a wireless GSM

electronic medication tray (MedMinder), is described elaborately by (McGillicuddy et al., 2013) in which a specific medication compartment blinks up on the correct day/time when medication needs to be taken followed by an audio reminder signal with an extra reminder by phone or text message send to the patient. A comparable principle of electronic medication dispenser (with visual and audible signals), in which medication usage is monitored through a web-based application, was used by (Henriksson et al., 2016). Wireless pill bottles (Vitality GlowCap), with customized reminders (not limited to alarms, text messages, phone calls with recorded messages and emails) and physician notifications were described as an intervention in the study of (Reese et al., 2017). The Way to Health Platform was used as an overall platform provider to monitor treatment adherence.

3.2.3 Sample characteristics

Total sample size of the included studies represents 266 kidney transplant patients ranging from *n*=19 to *n*=120 between the different trials. One study focusses on hypertensive kidney transplant patients (McGillicuddy et al., 2013). Two studies focus on adult patients (> 18 years old) with a mean age of 42.4 (SD=12.0)(McGillicuddy et al., 2013) and 50.0 (SD=11.0) (Reese et al., 2017). Except for one study (Reese et al., 2017), participants were within 1 year of their transplantation and represented a mixture between living and deceased donors (Henriksson et al., 2016; Reese et al., 2017; Schmid et al., 2017). There was a slight overrepresentation of men (*n*=160; 60.2%) in the included studies.

3.2.4 Intervention content and duration

Telemedicine (Schmid et al., 2017) and electronic / wireless drug dispensers or medication trays (Henriksson et al., 2016; McGillicuddy et al., 2013; Reese et al., 2017) were used to improve kidney transplant outcomes with an intervention duration ranging from 3 months to

1 year. Three studies accounted for participants' digital literacy level (Henriksson et al., 2016; McGillicuddy et al., 2013; Reese et al., 2017), from which one set it as an inclusion criteria (McGillicuddy et al., 2013).

3.3 Quality Appraisal of individual studies

Table 2 presents agreed quality assessment results of the individual RCTs based on CASP checklist and SORT guidelines. This has been performed by two authors (KB, CB) independently. Results indicate low-quality studies with weak evidence for the effectiveness of eHealth interventions improving clinical outcomes in young kidney transplant patients. Although most studies formulated clear aims and objectives, prespecified hypotheses regarding treatment effects were missing. Most studies randomized patients across different treatment conditions including active and non-active control groups. Only one study performed an intention-to-treat analysis with other studies remaining unclear how they treated drop-out in their analyses. Some statistics (e.g., confidence intervals, effect sizes) were missing and in most cases the statistician running the analyses was the only element blinded across the studies. It was unclear if a pre-specified Statistical Analysis Plan (SAP) had been used across the studies even though all trials were registered. Overall, it cannot be ascertained effects seen in some of the self-management, treatment adherence and clinical outcomes across young kidney transplant patients can actually be attributed to the eHealth intervention. All studies were classified as Level 2 (low-quality) based on the SORT guidelines. The overall "Strength of Recommendation" was Level B given that no high-quality (Level 1) studies were identified.

(Insert Table 2 here)

Journal Pre-proof

3.4 Synthesis of primary and secondary study results

Based on thematic analyses, study results are presented alongside four overarching (clinical, psychological, resource use and intervention user views) and 18 subthemes (see Figure 2). See Table 3 on how these outcomes were assessed and Table 4 for treatment effects, CIs and effect sizes.

(Insert Figure 2 black/white, Table 3 and Table 4 here)

3.4.1 Clinical

Adherence

Three studies (Henriksson et al., 2016; McGillicuddy et al., 2013; Reese et al., 2017) included treatment adherence to immunosuppressive medication as the primary outcome measure and one study (Schmid et al., 2017) included this outcome as a secondary outcome measure. One study (Henriksson et al., 2016) indicates a high compliance rate when using the electronic monitoring drug dispenser for 1 year but with more missed doses across specific groups. Another study (McGillicuddy et al., 2013) demonstrates an improvement in treatment adherence when using the prototype mHealth system over a 3-months period compared to standard care alone. Furthermore, another study (Reese et al., 2017) reports a significant difference in Tacrolimus adherence between treatment and control groups during the last 90 days of the study with the highest increase among participants in the pill bottle plus reminders and notification group. Pharmacists stressed their concerns about treatment adherence for the majority of patients. Finally, one study (Schmid et al., 2017) indicated that participants in standard care appeared to be less adherent compared to participants who received telemedicine over the 1-year study period.

Journal Pre-proof

Hospital admissions

There was no difference between the intervention and control cases regarding emergency hospital admissions in one study (Henriksson et al., 2016). In another study (Schmid et al., 2017), there were fewer hospital admissions (as a primary outcome measure) and a shorter length of unplanned hospital stay of patients supported by telemedicine compared to standard care. Finally, one study (Reese et al., 2017) mentioned they documented the number of hospitalizations but do not present the results.

Ambulatory care

There were no differences in the total amount of planned outpatient follow-up visits between the intervention and control groups within two studies (Henriksson et al., 2016; Schmid et al., 2017).

Rejection rate

There was no difference in the number of rejections between the intervention and control group in one study (Henriksson et al., 2016). More rejections occurred during the first six months of the study period. Also, the p-creatinine level is not related to rejections and there was no difference between patients who used different types of medicine to treat rejection episodes over time. In another study (Schmid et al., 2017), the number of acute rejections was too low to make reliable group comparisons.

Adverse events

Serious and medical device related adverse events were reported to the electronic medication dispenser manufacturer during one study (Henriksson et al., 2016).

Journal Pre-proof

Blood pressure

Systolic blood pressure was lower in participants across the mHealth condition during the first and third month compared to the control condition. Diastolic blood pressure values were higher for participants in the mHealth condition at baseline and third month compared to the control condition (McGillicuddy et al., 2013).

Estimated Glomerular Filtration Rate

Based on eGFR, there was no median difference for change between telemedicine and standard care groups regarding transplant functioning over 1-year period (Schmid et al., 2017).

Length of time before rejection therapy initiation

This outcome measure was described but not reported accordingly (Schmid et al., 2017).

Graft loss

Two patients lost their graft before baseline but none during the study (Henriksson et al., 2016). Also, in another study there were two cases of graft loss across the standard care condition (Schmid et al., 2017).

Death

One participant died during the study but this was unrelated to study procedures (Reese et al., 2017).

Kidney failure

Journal Pre-proof

One participant suffered from kidney failure during the study but this was unrelated to study procedures (Reese et al., 2017).

3.4.2 Psychological

QoL

Health-related QoL improved across telemedicine and standard care groups over the year with a most pronounced different on disease-specific QoL after 9 and 12 months (Schmid et al., 2017).

Psychological distress

Psychological distress significantly decreased over the year across both conditions (Schmid et al., 2017).

3.4.3 Resource use

Costs of rejection

Participants not using an electronic medication dispenser displayed higher hospital costs as a consequence of transplant rejection (Henriksson et al., 2016).

Hospital costs

A lower amount of hospital admissions and stay were associated with inpatient care savings (Schmid et al., 2017).

Return to work

Journal Pre-proof

Compared to standard care, participants who received telemedicine returned back to full employment quickly after discharge and this remained stable throughout 1-year study duration (Schmid et al., 2017).

3.4.4 Intervention User Views

Acceptability

Participants were highly satisfied with the prototype mHealth system but with some of them finding it too bulky (McGillicuddy et al., 2013). Medication reminders seemed to be appreciated but specific results were not presented (Reese et al., 2017).

Feasibility

Participants found the prototype mHealth system easy to use at home and supportive for their medication and health management (McGillicuddy et al., 2013). Some participants had difficulties with integrating pill bottle usage into their daily medication taking routine with a majority of them experiencing pill bottle errors (Reese et al., 2017).

4 Discussion

4.1 Summary of evidence

The aim of this systematic review was to gather existing evidence on eHealth interventions to improve self-management primarily and treatment adherence as well as clinical outcomes in young kidney transplant patients and assessing overall study quality. This resulted in four RCT studies, mainly examining mHealth applications and electronic pill dispensers, using reminders and notifications across the general kidney transplant population (mostly above 18 years old). Dividing outcomes into clinical, psychological, resource use and intervention user views themes resulted in a strong overrepresentation of clinical outcomes. In all studies,

adherence improved more across the intervention group compared to the standard care group with the most pronounced treatment effect in one study (Schmid et al., 2017) using Intention-To-Treat analysis and assessing adherence through a summarized adherence score of self-report, collateral reports and Tacrolimus levels. However, given that none of the studies included pre-specified hypotheses and were primarily non-blinded no reliable overall conclusion can be drawn about effectiveness and additionally other measures of adherence (i.e. Tacrolimus blood concentrations, self-report) were demonstrating contradicting results (Reese et al., 2017). Future studies should go beyond short-term group-level comparisons as small significant effects of eHealth interventions on adherence do not necessarily indicate clinically relevant results.

Two studies (Henriksson et al., 2016; Schmid et al., 2017) indicated lower amounts of hospital admissions in the intervention group compared to the standard care group up till 1 year after transplant, but no differences regarding ambulatory hospital visits. A trend was described in the number of emergency biopsies (assessing diagnosis of rejection) with higher numbers in the control group compared to the intervention group (Henriksson et al., 2016) but in another study (Schmid et al., 2017) sample numbers were too low to make reliable comparisons. Pilot results (McCullicuddy et al., 2013) demonstrated lower systolic blood pressure among participants who used the prototype mHealth system. Given its exploratory nature and small sample size no robust conclusions can be drawn. No adverse events were reported across studies and no differences between telemedicine and control groups regarding eGFR levels 1-year post transplant were reported (Schmid et al., 2017). Across the studies, one participant passed away (Reese et al., 2017), one participant suffered from kidney failure and two participants lost their grafts (Schmid et al., 2017) but this was unrelated to study procedures. The remaining clinical, psychological, resource use and intervention user views themed outcomes showed positive trends but were incomplete in terms of statistical

comparison and reported statistical values. Even though studies were registered in clinical trial registries, they were all scored as low-quality according to CASP and SORT guidelines thereby preventing the study to draw any sort of conclusion regarding the effect of eHealth interventions on self-management, adherence and clinical outcomes in young kidney transplant patients.

4.2 Future recommendations

To build up the evidence in this research area, the current review will need to be updated with initiatives evolved during and after COVID-19 pandemic. During this time, eHealth interventions and other digital approaches have massively grown as solutions providing care to vulnerable patients while struggling with staff shortages (Webster, 2020). This review calls for an improvement of studies in this field. Most studies were lacking pre-defined hypothesis, did not adhere to a SAP, were non-blinded and did not include a representative sample with nonadherent patients. More rigorous and high-quality studies will advance this field by enabling researchers to calculate pooled effects of eHealth interventions on a variety of outcomes for young kidney transplant patients. The same is true for studies examining the effectiveness of eHealth interventions in related populations e.g., chronic kidney disease. A Cochrane review (Stevenson et al., 2019) demonstrated improvement in dietary outcomes (e.g., sodium, fluid intake) across an adult population but evidence was rated as low due to high or unknown risk of bias across studies. Heterogeneity in intervention type and components made it impossible to conclude what elements of eHealth interventions are effective in this population.

As long as there is no unified definition and “golden standard” of measuring adherence, it makes it challenging for researchers and clinicians to summarize treatment effects across studies and draw definite conclusions what works for this population (Dobbels

et al., 2010). It has been suggested that Tacrolimus is not adequately captured by measuring it in blood concentrations due to variation with other clinical outcomes such as rejection (Reese et al., 2017). However, based on the current studies Tacrolimus seems to be the most objective assessment of adherence as pill bottle openings does not necessarily mean that patients actually take those pills, whereas self-reported adherence seems to reflect an overestimation (Reese et al., 2017). For future studies, it is recommended to use a combination of objective and subjective measures to assess (non)adherence with self-report questionnaire, lab report and clinician's observations having the highest sensitivity (72%) and specificity (42%) (Fine et al., 2009).

As indicated in previous studies (Haynes et al., 2008) the nature of adherence is complex but this was not reflected in any of the studies, except for one study (Schmid et al., 2017) in which case management and personalisation is offered through telemedicine. Expecting improvement of adherence and clinical outcomes from an electronic pill dispenser in nonadherent patients is unrealistic as they are highly likely to be non-adherent to elaborate procedures (Duncan et al., 2017). Innovative and well-designed advanced systems that include artificial intelligence might be able to tackle this by embedding it in a non-invasive unobtrusive way into their daily life. Monitoring automatically instead of relying on patient input for example through wearables could be part of the solution clinicians and researchers face regarding non-adherent patients (Kooman et al., 2020). Additionally, given the fact that adolescence and young adulthood brings on its own challenges (e.g., independence, autonomy) this will need to be taken into account into future studies.

Although innovative eHealth interventions such as wearable devices are being developed, data privacy and security issues remain with the risk of successful cyberattacks capturing highly sensitive data (Kooman et al., 2020; Duettmann et al., 2021). Moreover, future studies need to take implementation strategies and cost-effectiveness of adherence

interventions into account from a patient as well as healthcare professional perspective. Implementation science remains underutilized with implementation aspects underreported across randomized controlled studies in transplantation. For future studies it is important to include information at study start on context, stakeholders, sample representativeness, feasibility and implementation strategies to ultimately support implementation in clinical care contexts (Kostalova et al., 2022). To ensure the development and successful long-term use of eHealth interventions, end-users and healthcare professionals should be involved from the beginning to prevent a mismatch in needs and solutions. There should be reliable internet access, devices should be provided, and training offered where needed. Patients appreciate flexibility regarding data access, fine-tuning of intervention content reflecting their unique experiences of transplant care and involvement of their social support system. Increased workload and costs should be avoided by integrating eHealth intervention into the existing workflow (Duettmann et al., 2021). However, this seems challenging with most healthcare systems being outdated and conservative in terms of their infrastructure. Financial reimbursement of eHealth interventions seems challenging across most conservative and resource lacking healthcare systems with a strong lack of evidence-base for eHealth interventions in transplant care complicating this even further (Duettmann et al., 2021).

4.3 Limitations

The current review followed the PRISMA 2020 reporting guidelines (see Supplemental File 1) as well as established quality appraisal checklists and tools which could be seen as a strength of this study. However, there are some significant limitations, and this study should therefore be interpreted in context of these shortcomings.

Firstly, results of this review present a small amount of studies all published before October 2020 reflecting the start of COVID-19 pandemic. Studies demonstrate limited

evidence-base characterized by low quality due to a small sample size (in relation to the amount of outcome measures) derived from one treatment centre, its preliminary character, no predefined SAP, different methods of measuring adherence and nonblinding of participants and study staff, increasing the chance of a positive bias towards effectiveness of the introduced technologies. Based on current searches across international trial registries and scientific databases it is clear that new usability, feasibility and effectiveness trials studies are on its way (Duettmann et al., 2021) which will give us a better understanding what is out there and more importantly what works for whom. More robust and high-quality randomized controlled trials should be performed, enabling researchers to build up the evidence base on the effects of eHealth interventions on self-management, adherence and clinical outcomes in young kidney transplant patients.

Secondly, included studies mainly reflect older participants as the condition is more prevalent among older patients. Future studies should address this by focussing on adolescent and young adult population given the implications of non-adherence in terms of graft survival and acute rejections (Foster et al., 2011). Also, two studies were only focussing on specific immunosuppressive drugs (Reese et al., 2017; Schmid et al., 2017). Although, this might not represent a fully representative sample other factors were representatively presented across the studies such as gender and inclusion of living and deceased donors as well as the use of convenient sampling (Duncan et al., 2017; McGillicuddy et al., 2013) preventing inclusion of patients who are adherent already which happens mostly during the first three months after hospitalization. For future studies it is important to include a representative sample consisting of adherent and non-adherent patients. Recruiting and engaging non-adherent patients can be challenging but can be supported through site selection considering patient characteristics, minimizing the burden of study procedures for patients, following sequential selection of eligible patients while monitoring characteristics of other eligible patients who were not

recruited, and compare primary outcome of adherence and other patient characteristics using an existing national database (Shemesh et al., 2017; Shemesh et al., 2020; Kostalova et al. 2022).

Thirdly, studies elaborate an earlier review performed in the field of transplantation (De Bleser et al., 2009) and resemble a recent review (Duncan et al., 2017) but contribute to the field through its specific focus on technology-based interventions in kidney transplant patients. Moreover, a more elaborate narrative review and critical quality appraisal are presented.

Finally, while the majority of the studies was focussed on treatment adherence and clinical outcomes, none of the studies assessed self-management. It is expected that self-managing a condition takes more time and guidance than was provided by the interventions of the included studies with a 1-year follow-up period (Newman et al., 2004). This is also confirmed by one study (Schmid et al., 2017) implying that there is more focus on acute care and case management during the first year instead of focussing on long-term goals such as sustaining adherence and self-managing a certain chronic condition.

5. Conclusions

This review stresses the need for more robust and high-quality studies with representative samples in the field of renal transplant before any firm conclusions can be drawn regarding the effectiveness of eHealth interventions for young patients on self-management, adherence and clinical outcomes. eHealth interventions aiming to improve clinical outcomes in young kidney transplant patients are available but still very limited in terms of quantity and quality. While new initiatives have been developed during and after COVID-19 pandemic, none of the reviewed studies are solely focussing on young kidney transplant patients or self-management outcomes implying that clinical outcomes in adult patients are currently still

prioritized. While care provision in the hospital directly after receiving the transplant seems of utmost importance, understanding reasons for non-adherence is crucial in improving adherence on the longer term while preventing adverse outcomes after one year of follow-up. More large-scale and rigorous research is needed before any conclusions can be drawn regarding the effectiveness of eHealth interventions for young kidney transplant patients.

Acknowledgements

I would like to thank Deborah Griggs for supporting us in gaining funding successfully for this project.

Funding

This work was financially supported by the WPH Charitable Trust. The funders did not have any role in the review.

Journal Pre-proof

References

Brice, R. (n.d.). CASP CHECKLISTS. *CASP - Critical Appraisal Skills Programme*. Retrieved 18 February 2022, from https://casp-uk.net/casp-tools-checklists/

Browning, R. B., McGillicuddy, J. W., Treiber, F. A., & Taber, D. J. (2016). Kidney transplant recipients' attitudes about using mobile health technology for managing and monitoring medication therapy. *Journal of the American Pharmacists Association*, *56*(4), 450-454.e1. https://doi.org/10.1016/j.japh.2016.03.017

Charlier, N., Zupancic, N., Fieuws, S., Denhaerynck, K., Zaman, B., & Moons, P. (2016). Serious games for improving knowledge and self-management in young people with chronic conditions: A systematic review and meta-analysis. *Journal of the American Medical Informatics Association*, *23*(1), 230–239. https://doi.org/10.1093/jamia/ocv100

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed). L. Erlbaum Associates.

De Bleser, L., Matteson, M., Dobbels, F., Russell, C., & De Geest, S. (2009). Interventions to improve medication-adherence after transplantation: a systematic review. *Transplant International*, 22(8), 780-797.

Duncan, S., Annunziato, R. A., Dunphy, C., LaPointe Rudow, D., Shneider, B. L., & Shemesh, E. (2017). A systematic review of immunosuppressant adherence interventions in transplant recipients: Decoding the streetlight effect. *Pediatric Transplantation*, *22*(1), e13086. https://doi.org/10.1111/petr.13086

Duettmann, W., Naik, M. G., Zukunft, B., Osmonodja, B., Bachmann, F., Choi, M., ... & Budde, K. (2021). eHealth in transplantation. *Transplant International*, *34*(1), 16-26.

Dobbels, F., Ruppar, T., De Geest, S., Decorte, A., Van Damme-Lombaerts, R., &

Fine, R. N. (2010). Adherence to the immunosuppressive regimen in pediatric kidney transplant recipients: a systematic review. *Pediatric transplantation*, 14(5), 603-613.

Ebell, M. H., Siwek, J., Weiss, B. D., Woolf, S. H., Susman, J., Ewigman, B., & Bowman, M. (2004). Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *The Journal of the American Board of Family Practice*, *17*(1), 59-67.

Fine, R. N., Becker, Y., De Geest, S., Eisen, H., Ettenger, R., Evans, R., ... & Dobbels, F. (2009). Nonadherence consensus conference summary report. American Journal of Transplantation, 9(1), 35-41.

Foster, B. J., Dahhou, M., Zhang, X., Platt, R. W., Samuel, S. M., & Hanley, J. A. (2011). Association Between Age and Graft Failure Rates in Young Kidney Transplant Recipients. *Transplantation*, *92*(11), 1237–1243. https://doi.org/10.1097/TP.0b013e31823411d7

Fredericks, E. M., & Dore-Stites, D. (2010). Adherence to immunosuppressants: How can it be improved in adolescent organ transplant recipients?: *Current Opinion in Organ Transplantation*, *15*(5), 614–620. https://doi.org/10.1097/MOT.0b013e32833d3115

Han, A., Cho, M.-J., Cho, S., Lee, C. H., Choi, C., Kim, S.-Y., Hong, H., Ahn, S., Min, S.-K., & Min, S.-I. (2016). Use of mobile internet application to improve adherence to immunosuppressive medication adherence in kidney transplant recipients: Preliminary results of the PRIMA (ImPRoving Adherence to Immunosuppressive Therapy by Mobile Internet Application) study. *Transplantation*, *100*(7), S161–S161.

Haynes, R. B., Ackloo, E., Sahota, N., McDonald, H. P., & Yao, X. (2008). Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD000011.pub3

Journal Pre-proof

Henriksson, J., Tydén, G., Höijer, J., & Wadström, J. (2016). A Prospective Randomized Trial on the Effect of Using an Electronic Monitoring Drug Dispensing Device to Improve Adherence and Compliance. *Transplantation*, *100*(1), 203–209. https://doi.org/10.1097/TP.0000000000000971

Kooman, J. P., Wieringa, F. P., Han, M., Chaudhuri, S., van der Sande, F. M., Usvyat, L. A., & Kotanko, P. (2020). Wearable health devices and personal area networks: can they improve outcomes in haemodialysis patients? *Nephrology Dialysis Transplantation*, 35(Supplement_2), ii43-ii50.

Korus, M., Cruchley, E., Stinson, J. N., Gold, A., & Anthony, S. J. (2015). Usability testing of the Internet program: "Teens Taking Charge: Managing My Transplant Online". *Pediatric Transplantation*, *19*(1), 107–117. https://doi.org/10.1111/petr.12396

McGillicuddy, J. W., Gregoski, M. J., Weiland, A. K., Rock, R. A., Brunner-Jackson, B. M., Patel, S. K., Thomas, B. S., Taber, D. J., Chavin, K. D., Baliga, P. K., & Treiber, F. A. (2013). Mobile Health Medication Adherence and Blood Pressure Control in Renal Transplant Recipients: A Proof-of-Concept Randomized Controlled Trial. *JMIR Research Protocols*, *2*(2), e32. https://doi.org/10.2196/resprot.2633

Moons, P., Vanrenterghem, Y., Hooff, J. P., Squifflet, J.-P., Margodt, D., Mullens, M., Thevissen, I., & Geest, S. (2003). Health-related quality of life and symptom experience in tacrolimus-based regimens after renal transplantation: A multicentre study. *Transplant International*, *16*(9), 653–664. https://doi.org/10.1111/j.1432-2277.2003.tb00366.x

Nerini, E., Bruno, F., Citterio, F., & Schena, F. P. (2016). Nonadherence to immunosuppressive therapy in kidney transplant recipients: can technology help? *Journal of Nephrology*, 29, 627-636.

Journal Pre-proof

Newman, S., Steed, L., & Mulligan, K. (2004). Self-management interventions for chronic illness. *The Lancet*, *364*(9444), 1523–1537. https://doi.org/10.1016/S0140-6736(04)17277-2

Nguyen, C., Dew, M. A., Irizarry, T., McNulty, M., Rennick, J., Knäuper, B., Descoteaux, A., Grenier, A., Jeannot, L., Foster, B. J., DeVito Dabbs, A. J., & all TAKE-IT TOO Investigators. (2020). Promoting medication adherence from the perspective of adolescent and young adult kidney transplant recipients, parents, and health care professionals: A TAKE-IT TOO study. *Pediatric Transplantation*, *24*(5). https://doi.org/10.1111/petr.13709

Osterberg & Blaschke. (2005). Adherence to Medicine. *The New England Journal of Medicine*, *335*(5).

Pinson, C. W., Feurer, I. D., Payne, J. L., Wise, P. E., Shockley, S., & Speroff, T. (2000). Health-Related Quality of Life After Different Types of Solid Organ Transplantation: *Annals of Surgery*, *232*(4), 597–607. https://doi.org/10.1097/00000658-200010000-00015

Popay, J., Roberts, H., Sowden, A., Petticrew, M., Arai, L., Rodgers, M., & Britten, N. (2006). *Guidance on the Conduct of Narrative Synthesis in Systematic Reviews*. 92.

Prendergast, M. B., & Gaston, R. S. (2010). Optimizing Medication Adherence: An Ongoing Opportunity To Improve Outcomes After Kidney Transplantation. *Clinical Journal of the American Society of Nephrology*, *5*(7), 1305–1311. https://doi.org/10.2215/CJN.07241009

Reese, P. P., Bloom, R. D., Trofe-Clark, J., Mussell, A., Leidy, D., Levsky, S., Zhu, J., Yang, L., Wang, W., Troxel, A., Feldman, H. I., & Volpp, K. (2017). Automated Reminders and Physician Notification to Promote Immunosuppression Adherence Among

Journal Pre-proof

Kidney Transplant Recipients: A Randomized Trial. *American Journal of Kidney Diseases*, *69*(3), 400–409. https://doi.org/10.1053/j.ajkd.2016.10.017

Rianthavorn, P., & Ettenger, R. B. (2005). Medication non-adherence in the adolescent renal transplant recipient: A clinician's viewpoint. *Pediatric Transplantation*, *9*(3), 398–407. https://doi.org/10.1111/j.1399-3046.2005.00358.x

Rovelli, M., Palmeri, D., Vossler, E., Bartus, S., Hull, D., & Schweizer, R. (1989). Noncompliance in organ transplant recipients. *Transplantation Proceedings*, *21*(1 Pt 1), 833–834.

Sabaté, E., & World Health Organization (Eds.). (2003). *Adherence to long-term therapies: Evidence for action*. World Health Organization.

Schmid, A., Hils, S., Kramer-Zucker, A., Bogatyreva, L., Hauschke, D., De Geest, S., & Pisarski, P. (2017). Telemedically Supported Case Management of Living-Donor Renal Transplant Recipients to Optimize Routine Evidence-Based Aftercare: A Single-Center Randomized Controlled Trial. *American Journal of Transplantation*, *17*(6), 1594–1605. https://doi.org/10.1111/ajt.14138

Shellmer, D. A., Dabbs, A. D., Dew, M. A., & Mazariegos, G. (2011). DEVELOPMENT AND USABILITY OF TEEN POCKET PATH (R) A MOBILE HEALTH APPLICATION TO PROMOTE SELF-CARE AMONG ADOLESCENT ORGAN TRANSPLANT RECIPIENTS. *PEDIATRIC TRANSPLANTATION*, *15*, 72–72.

Shellmer, D. A., Dew, M. A., Mazariegos, G., & DeVito Dabbs, A. (2016). Development and field testing of Teen Pocket PATH ®, a mobile health application to improve medication adherence in adolescent solid organ recipients. *Pediatric Transplantation*, *20*(1), 130–140. https://doi.org/10.1111/petr.12639

Shemesh, E., Mitchell, J., Neighbors, K., Feist, S., Hawkins, A., Brown, A., ... & Annunziato, R. A. (2017). Recruiting a representative sample in adherence

Journal Pre-proof

research—The MALT multisite prospective cohort study experience. *Pediatric transplantation, 21*(8), e13067.

Shemesh, E., Shneider, B. L., & Mazariegos, G. V. (2020). Weekend versus weekday adherence: Do we, or do we not, thank God it's Friday? *American Journal of Transplantation, 20*(1), 7-9.

Sinnya, S., Finnane, A., & Soyer, H. P. (2015). Use of mobile app for patient information in solid organ transplantation—Minimising gaps in patient education. *Australasian Journal of Dermatology*, *56*, 68–68. https://doi.org/10.1111/ajd.12337

Sketris, I., Waite, N., Grobler, K., West, M., & Gerus, S. (1994). Factors affecting compliance with cyclosporine in adult renal transplant patients. *Transplantation Proceedings*, *26*(5), 2538–2541.

Stevenson, J. K., Campbell, Z. C., Webster, A. C., Chow, C. K., Tong, A., Craig, J. C., ... & Lee, V. W. (2019). eHealth interventions for people with chronic kidney disease. Cochrane Database of Systematic Reviews, (8).

Subho Chakrabarti. (2014). *What's in a name? Compliance, adherence and concordance in chronic psychiatric disorders*. *4*(2), 30–36. https://doi.org/10.5498/wjp.v4.i2.30

Taber, D. J., Pilch, N. A., McGillicuddy, J. W., Mardis, C., Treiber, F., & Fleming, J. N. (2019). Using informatics and mobile health to improve medication safety monitoring in kidney transplant recipients. American Journal of Health-System Pharmacy, 76(15), 1143-1149.

the TAKE-IT Study Group, Foster, B. J., Pai, A., Zhao, H., & Furth, S. (2014). The TAKE-IT study: Aims, design, and methods. *BMC Nephrology*, *15*(1), 139. https://doi.org/10.1186/1471-2369-15-139

Webster, P. (2020). Virtual health care in the era of COVID-19. *The*

Journal Pre-proof

lancet, *395*(10231), 1180-1181.

Wüthrich, R. P., Eisenberger, U., Bock, A., Ambühl, P., Steiger, J., Intondi, A., Kuranoff, S., Maier, T., Green, D., Feutren, G., & De Geest, S. (2012). Towards a Gold Standard for Adherence Assessment in Transplantation: High Accuracy of the Proteus Raisin System (PRS) Combined with Enteric-Coated Mycophenolate Sodium (ECMPS) in Stable Kidney Transplant Recipients: 625. *Transplantation Journal*, *94*(10S), 245. https://doi.org/10.1097/00007890-201211271-00456

Zhu, Y., Zhou, Y., Zhang, L., Zhang, J., & Lin, J. (2017). Efficacy of interventions for adherence to the immunosuppressive therapy in kidney transplant recipients: A meta-analysis and systematic review. *Journal of Investigative Medicine*, *65*(7), 1049–1056. https://doi.org/10.1136/jim-2016-000265

Journal Pre-proof

Table 1. Summary of included studies focusing on eHealth to improve self-management, treatment adherence and clinical outcomes among adolescents and young adults following renal transplantation (n=4).

Citation	Aim	Design	Country	Sample size	Participant description & Age	Intervention & Duration	Primary outcomes	Secondary outcomes
Henriksson, J., Tydén, G., Höijer, J., & Wadström, J. (2016). A prospective randomized trial on the effect of using an electronic monitoring drug dispensing device to improve adherence and compliance. *Transplantation*, *100*(1), 203-209.	Examine effects of Electronic Monitoring Drug Dispenser	Prospective randomized trial with intervention and TAU control group	Sweden	N=80	Renal transplant patients; aged 22 - 69 years; 28 female / 52 male	Electronic Monitoring Drug Dispenser, web-based electronic medication dispenser (with visual and audible signals), 1 year	Medicine adherence	Emergency hospital admissions, number of biopsies to diagnose rejection, costs of rejection, number of missed outpatient follow-up visits, average level of p-creatinine, number of graft loss, medical

Journal Pre-proof

								device-related adverse events, (serious) adverse events
McGillicuddy, J. W., Gregoski, M. J., Weiland, A. K., Rock, R. A., Brunner-Jackson, B. M., Patel, S. K., ... & Treiber, F. A. (2013). Mobile health medication adherence and blood pressure control in renal transplant recipients: a proof-of-concept randomized controlled trial. *JMIR research protocols*, *2*(2).	Assess feasibility, acceptability and preliminary effectiveness of prototype mHealth system	Proof-of-Concept RCT with intervention and TAU control groups	USA	N=19	Kidney transplant patients, Mean age 42.44 (SD=12.04) intervention group, Mean age 57.6 (SD=8.28) control group; 8 female / 11 male	Prototype smartphone enabled mHealth system, wireless GSM electronic medication tray (MedMinder) with visual prompts and audio, phone or text message reminder, 3 months	Medication adherence, resting blood pressure	Acceptability, feasibility

Journal Pre-proof

Reese, P. P., Bloom, R. D., Trofe-Clark, J., Mussell, A., Leidy, D., Levsky, S., ... & Feldman, H. I. (2017). Automated reminders and physician notification to promote immunosuppression adherence among kidney transplant recipients: a randomized trial. *American Journal of Kidney Diseases*, *69*(3), 400-409.	(1) Examine effects of automated reminders and physician notifications in increasing immunosuppressive adherence compared to monitoring alone (2) Examine accuracy of pharmacists predictions of each participant's adherence	RCT with reminder (arm 1), reminder plus notification (arm 2) and wireless pill bottle use (control group; arm 3)	USA	N=120	Kidney transplant recipients, Mean age 50.0 (SD=11.0); 43 female / 72 male	Wireless pill bottle (Vitality GlowCap) with automated and customized reminders (not limited to alarms, text messages, phone calls with recorded messages and emails) AND physician notifications on Way to Health Platform, 6 months	Percentage of correctly taken tacrolimus doses (as measured by pill bottles opening, blood concentrations and self-report)	Adverse events, number of hospitalizations, qualitative data about technology appreciation and ease of use, pill bottle / user errors, death, kidney failure, pharmacist adherence prediction

Journal Pre-proof

Schmid, A., Hils, S., Kramer-Zucker, A., Bogatyreva, L., Hauschke, D., De Geest, S., & Pisarski, P. (2017). Telemedically supported case management of living-donor renal transplant recipients to optimize routine evidence-based aftercare: a single-center randomized controlled trial. *American Journal of Transplantation*, *17*(6), 1594-1605.	Assess effectiveness of telemedically supported case management during the first transplant year	Prospective, open-label, randomized comparative effectiveness study with repeated-measures design; TAU + telemedically supported case management AND TAU groups	Germany	N=46	Renal transplant recipients; aged 8 - 59 years; 21 female / 25 male	Telemedically supported case management (consisting of three elements), 1 year	Unplanned admission rate	Length of unplanned stay, unplanned inpatient care costs in Euros, rejection rate, length of time before rejection therapy initiation, estimated glomerular filtration rate (eGFR), ambulatory care visit rate, composite adherence score (CAS) and CAS percentage grade, psychologi

Journal Pre-proof

								cal and quality-of-life questionnaires subscale scores, working time percentage

*TAU=Treatment As Usual

Journal Pre-proof

Table 2. Summarized Quality Appraisal of Individual RCTs based on CASP checklist and SORT guidelines.

	CASP											SORT
Study	1. Did the study address a clearly focused research question?	2. Was the assignment of participants to interventions randomised?	3. Were all participants who entered the study accounted for at its conclusion?	4. Were participants, investigators and people assessing/analysing outcomes "blinded"?	5. Were the study groups similar at the start of the randomised controlled trial?	6. Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?	7. Were the effects of intervention reported comprehensively?	8. Was the precision of the estimate of the intervention or treatment effect reported?	9. Do the benefits of the experimental intervention outweigh the harms and costs?	10. Can the results be applied to your local population/in your context?	11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	Level of Evidence
Henrikson et al., (2016)	Can't tell	Yes	Yes	No	Yes	Can't tell	Can't tell	No	Yes	Can't tell	Yes	2
McGillicuddy et al., (2013)	Yes	Can't tell	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	2

Journal Pre-proof

Reese et al., (2017)	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	2
Schmid et al., (2017)	Yes	Yes	Yes	No	Yes	Yes	Yes	Can't tell	Can't tell	Can't tell	Yes	2

Journal Pre-proof

Table 3. Outcomes assessment across included studies categorized among themes and subthemes.

Source	Clinical											Psychological		Resource use			Intervention user views	
	Adherence	**Hospital admissions**	**Ambulatory care**	**Rejection**	**Adverse events**	**Blood pressure (BP)**	**eGFR***	**Length of time before rejection therapy initiation**	**Graft loss**	**Death**	**Kidney failure**	**QoL****	**Psychological distress**	**Costs of rejection**	**Hospital costs**	**Work time %**	**Acceptability**	**Feasibility**
Henriksson et al., (2016)	Number of missed medicine doses (Prograf or Advagraf) taken from EMD web-based software	Number of emergency hospital admissions with specified reasons	Missed scheduled outpatient follow-up visits	Number of emergency renal biopsies to diagnose rejection (based on Banff classification), level of p-	Serious adverse events, medical device related adverse event				Number of graft loss					Costs per rejection (in Swedish Kr on a)				

Journal Pre-proof

				creatinine	s													
McGillicuddy et al., (2013)	Average adherence score per month calculated with Russell et al. (2006), dose taken within 3-hour window (=adherent; 1.0), dose taken within 3 to 6-hour time window (=0.5), missed dose (=nonadherent;0.0)					Use of FORAD15 device at home (with protocol), average of last two readings, same day measurements by registered nurse in case BP value is not available											(No) acceptance to participate in mHealth or standard care protocol including reasons	Easy to learn how to use mHealth system (5-point Likert scale), easy to use mHealth system at home (5-point Likert scale), mHealth system is useful for medication/ health management (5-point Likert scale)
Reese et	Pill bottle	Number			Serio					Numb	Numb						Qualitati	Qualitative

Journal Pre-proof

al., (2017)	openings over final 90 days, pill bottle openings between 14 days and study end, coefficient of variation of tacrolimus blood concentrations as measured by protocol, coefficient of variation of any morning tacrolimus blood concentration measur	of hospitalizations at week 5, 9 and 17			us adverse events					er of participants who died	er of participants with kidney failure						ve expression of appreciation by participants about medication reminders	report about not having difficulty with using pill bottles in their daily routine, pill bottle and/or user error as assessed by study coordinator

Journal Pre-proof

	ed for any indication, 5-item self-report Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS) at study end, pharmacist adherence prediction at study start "I am concerned that this patient will have difficulty with immun																	

Journal Pre-proof

	osuppressive medication adherence" with 5-point Likert scale (strongly disagree to strongly agree)																
Schmidet al., (2017)	Transcoding into fully adherent, partial adherent and nonadherent based on Self-Report in the Basel Assessment of Adherence to Immunosuppressive Medic	Sum of unplanned hospital admissions according to all medical reports, sum of unplanned inpatient days according to all	Sum of ambulatory care visits (outpatient clinic and resident physicians) according to all physician	Sum of biopsy-proven acute rejections rate			Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations with serum creatinine level in medical	Sum of days between first creatinine level increase before a biopsy-proven rejection and the start of glucocorticoid	Number of graft loss			Fragebogen Alltagsleben (ALL), End-Stage Renal Disease Symptom Checklist-Transplantation Module (ESRD-	Brief Symptom Inventory 18 (BSI-18)		Sum of unplanned inpatient care costs according to fixed price system in Germa	Closed-ended question about working time percentage		

Journal Pre-proof

	ations Scale (BAASIS), two collateral reports (physicians, nurses), hit of target tacrolimus trough levels (ng/mL)	medical reports	reports				report	therapy according to the patient charts				SCL^{TM})			ny			
Number of studies with outcomes in subtheme	4	3	2	2	2	1	1	1	2	1	1	1	1	1	1	1	1	2	2
Number of studies with outcomes in overarching	4											1		2			2		

Journal Pre-proof

them e				

*estimated Glomerular Filtration Rate **Quality of Life

Journal Pre-proof

Table 4. Descriptive and inferential results (including statistics) per outcome measure across included studies.

Study	**Descriptive results**	**Inferential results including its statistics i.e.** **(mean difference, odds ratio, 95% confidence interval, effect size, p-value)**
Henriksson et al. (2016)	Compliance rate of 97.8% (with 2.2% missed doses 524/23820). More missed doses among 16 to 35-year olds (accounted for 48% of missed doses) and women (accounted for 60% of missed doses). Out of 53 emergency hospital admissions, 22 took place in the intervention group. A total amount of 22 scheduled outpatient follow-up visits (per patient) were reported during the first year after transplantation. Six patients missed a total amount of 11 visits, 8 from patients using the electronic monitoring drug dispenser and 3 from patients following standard care, representing 1% of the total amount of planned outpatient follow-up visits with no significant between-group differences. More rejections occurred during the first six months of the study period (82%; 27/33). Total costs of 6 rejections in the intervention group is 542.202 Swedish Krona versus (n=27) 2.439.909 Swedish Krona in the control group, which represents 4 times higher costs. Costs for 1 rejection is 12 times higher than using the electronic medication dispenser for one year, 90.367 Swedish Krona	More missed doses in evening (308/524; $p < 0.001$) and during last 6 months (303/524; $p < 0.001$) with a 20% increase in missed doses. The number of emergency hospital admissions did not differ between intervention group and control cases ($p = 0.854$). A total of 33 rejections were diagnosed across patients who used the electronic monitoring drug dispenser (n=6 among 4 participants) and standard care groups (n=27 among 13 participants). This difference was significant on univariate level (p=0.019) but not significant on multivariate level (p=0.054) when other variables were taken into account over time. There was no significant difference between the intervention and control groups who were using different types of medicine to treat rejection episodes over time (p=0.098).

Journal Pre-proof

	versus 7500 Swedish Krona. This includes costs associated with 3 days of inpatient care, radiographic study, pathology analysis, sampling, and the medication Solu-Medrol. Treatment costs of Thymoglobulin (4 days) is 35.985 Swedish Krona.	
Mcgillicuddy et al. (2013)	Posthoc analyses indicated that systolic blood pressure was lower in participants across the mHealth condition during the first (129.70) and third month (121.80) compared to the control condition (147.22 and 138.78). However, regarding the diastolic blood pressure values seemed to be higher for participants in the mHealth condition at baseline (87.55) and third month (86.70) compared to the control condition (76.11 and 79.44). The overall satisfaction score of participants using the prototype mHealth system was 4.8 (out of 5; with higher score indicating higher satisfaction). Participants reported on feasibility and demonstrated it was easy (4.7/5) for them to learn how to use the prototype mHealth system, to use it at home (4.8/5) and how supportive it was in medication and health management (4.3/5).	Improvement in treatment adherence when using the prototype mHealth system over a 3-months period compared to standard care alone ($F_{3, 48}$=11.74; $p < 0.001$; η_{p2}=.42). An average improvement from 0.576 (SE=0.048; 95% CI=0.474-0.677) to 0.945 (SE=0.037; 95% CI=0.865-1.025) in treatment adherence over time was reported for the intervention group ($F_{3, 48}$=32.81; $p < 0.001$; η_{p2}=.67). Differences in blood pressure were reported among the two groups over time regarding systolic blood pressure ($F_{3,51}$=4.33, P=.009, partial η^2=.20) and diastolic blood pressure ($F_{3,51}$=4.58, p=.006, partial η^2=.212).
Reese et al. (2017)		A significant difference (95% CI= 10%-38% and 95% CI= 21%-46%; $p < 0.001$) in

Journal Pre-proof

		adherence to tacrolimus (based on pill bottle openings) between both treatment groups (reminders 78% and reminders plus notifications 88%) versus the pill bottle only control group (55%) during the last 90 days of the trial. The same results for both treatment (82% and 88%) versus control groups (58%) were observed during the 14th day till the end of the trial (increase by 23% 95% CI=11%-36%; increase by 30% 95% CI=18%-42%). During the last 90 days of the trial, the reminders plus notifications group showed a 10% marginally higher treatment adherence compared to the reminders group, 95% CI=0%-19%; $p = 0.05$. These groups did not differ from each other in terms of treatment adherence during the 14th day till the end of the trial ($p = 0.1$). Pharmacists' indicated treatment adherence concerns for the majority of the patient population, OR=0.22; 95% CI=0.06-0.72; $p < 0.05$; C statistic 0.726. No number of hospitalizations is reported.
Schmid et al. (2017)	The biopsy proven acute rejection rates for telemedicine care was 2 out of 73 and for standard care 1 out of 17. Based on the eGFR values there appeared to be no median difference for change between the telemedicine (+3.6 mL) and standard care (+0.6 mL) groups regarding transplant functioning over 1-year period. The	Participants in standard care (56.5%) appeared to be less adherent compared to participants who received telemedicine (17.4%) over the 1-year study period (p=0.013). This was also confirmed by the significant group x time interaction effect for median CAS percentage grading scores, F $(2.6, \infty) = 10.58$, $p < 0.001$ with significant

Journal Pre-proof

	significantly lower amount of hospital admissions (19 versus 48) and shorter hospital stay (139 versus 422) among participants receiving telemedicine compared to standard care is associated with inpatient care savings of €3417 per patient.	differences between all time points. Also, participants who received telemedicine were more treatment adherent compared to participants from the standard care condition at the end of the study, (median = 100%, IQR = 7) versus SOCG (median = 93%, IQR = 21.5), U = 71.5, p < 0.001, r = 0.62. There was a significant interaction effect between group x time (F (1.7, ∞) = 4.41, *p*=0.017) with post hoc analyses demonstrating fewer hospital admissions of patients supported by telemedicine (median = 0 admissions, interquartile range [IQR] = 1) compared to patients receiving standard care (median = 2 admissions, IQR = 2), *U*=132.5, *p*=0.002, *r*=0.44 at the end of the first year. Also, there was a significant interaction effect between group x time (F (1.7, ∞) = 3.8, *p* = 0.029) with post hoc analyses demonstrating a shorted length of unplanned hospital stay for patients supported by telemedicine (median = 0 days, IQR = 6) compared to patients receiving standard care (median = 13 days, IQR = 23), *U*=141.0, *p*=0.005, *r* =0.41 at the end of the first year. There were no differences between the telemedicine and control groups regarding the sum of ambulatory care visits at 12 months posttransplant, median = 43 visits, IQR = 22; median = 45 visits, IQR = 28, *U*=216.5,

Journal Pre-proof

		p=0.297. Participants from the telemedicine and standard care groups significantly differed on the subscale of cardiac and renal dysfunction as well as on the side effects of corticosteroids with an overall trend of decreased QoL issues regarding those subscales. This trend for disease-specific QoL was most pronounced at after 9 months (median = 0.14, IQR = 0.29 versus median = 0.29; IQR = 0.43) and 12 months (median = 0, IQR = 0.2 versus median = 0.4, IQR = 0.6], U = 133, p = 0.004, r = 0.42). Participants from the standard care group differed in returning back to work percentage between baseline (median = 50%, IQR = 100) and month 3 (median = 0%, IQR = 50; Z = 2.694, p = 0.006, r = 0.4) and did not demonstrated full return within 1 year whereas participants offered telemedicine did.

Journal Pre-proof

Conflict of Interest
The authors declare there is no conflict of interest.

Journal Pre-proof

Highlights

- Treatment adherence is challenging in young kidney transplant patients
- eHealth can support adherence during this major life transition
- More high-quality RCTs should be designed to validate digital self-management approaches

Journal Pre-proof

PRISMA 2009 Flow Diagram – Summary of six search engines (CINAHL, COCHRANE, EMBASE, MEDLINE, PSYCHINFO, SCOPUS)

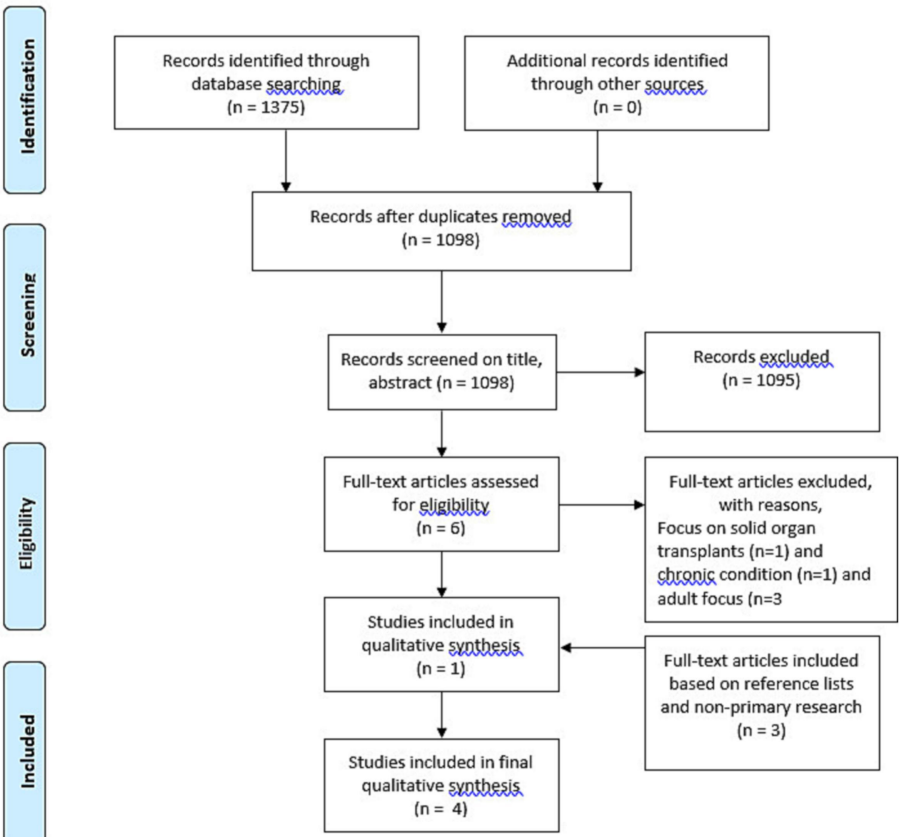

Figure 1


psychologicaldistress
kidneyfailure
costsofrejection
graftloss
ambulatorycare
hospitaladmissions
bloodpressure
adherence
egfr
acceptability
death
adverseevents
worktime
feasibility
qualityoflife
rejection
hospitalcosts
lengthoftimebeforerejectiontherapyinitiation

Figure 2