Effective Interventions and Patient Perceptions on the Management of Medication Adherence: a focus on mHealth

Thesis

Elyssa Katlin Wiecek

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University of Technology Sydney

CERTIFICATE OF ORIGINAL AUTHORSHIP

I Elyssa Katlin Wiecek declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Graduate School of Health at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

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Abstract

Background

Non-adherence to medications remains a global crisis with high prevalence causing worsening health outcomes, increased morbidity, and even death. Multiple dimensions affect the medication-taking process ranging from patient-related determinants to health system causes. Many interventions to improve adherence have seen disappointingly modest improvements with the most effective strategies including multiple components. These interventions are normally delivered as a package without the full understanding of what are the most effective components. The Digital Revolution has put mHealth (mobile health) at the forefront of new, emerging tools for improved adherence. An approximate 200 new mHealth apps are added to the market each day with 46% of patients adapting mobile technology to improve their health in the previous twelve months. While the technical tools within apps such as dosage reminders have been proven effective, other components such as rewards and gamification have yet to be evaluated. The variety of components being offered also warrants an exploration of the opinions of their users. Through understanding effectiveness by adherence outcomes and users' experiences within these mHealth offerings, a full understanding of their success and acceptability is possible.

Objectives

To explore, analyse and estimate the effect of interventions to improve medication adherence. This research aimed to gain a better understanding of the combination of components within effective interventions as well as evaluated an emerging mHealth tool, Perx Health. Simultaneously, beliefs, perceptions and experiences of users of the innovative mHealth intervention were explored to understand the acceptability and adoption of the technology.

Methodology

A series of discrete studies were undertaken: (1) a network meta-analysis of studies assessing the effectiveness of interventions and their components aimed at improving medication adherence; (2) evaluation of the impact of an innovative mHealth intervention, Perx, utilising multiple components on sustaining optimal adherence levels; and (3) analysis of users' beliefs, perceptions and experiences within the mHealth app for an understanding of the app's desirability and adoption as a tool to improve adherence.

Results

The network meta-analysis identified 249 studies evaluating interventions to improve adherence over multiple periods of time. Multicomponent interventions were found to the be the most effective interventions at improving adherence over 10 months, with education in combination with technical and attitudinal components (OR 0.49, 95% CrI 0.27-0.88) and rewards in combination with technical interventions having the most effective odds ratio (OR 0.03, 95% CrI 0.01-0.13) against standard of care. The Perx mHealth app utilising rewards, technical components, education and attitudinal components revealed high rates of adherence, average at 87.6% (SD 16.9%), above an optimal adherence threshold standard of 80%, over 6 months. An analysis of 6,296 user reviews of the mHealth app discovered a highly accepted and appreciated tool for aiding the management of medication adherence. Users reacted positively to reminder and reward components specifically, though expected improvements within technical functionality issues and the frequency of rewards.

Conclusion

Interventions to improve medication adherence have revealed modest improvements in effectiveness, with a continued need for multicomponent interventions to sustain adherence over 10 months. The evaluated mHealth intervention, Perx, utilising multiple components, including rewards, technical, education and attitudinal components, highlighted an intervention able to sustain optimal adherence rates over time. User reviews recognised a highly desirable and appreciated mHealth intervention in aiding the management of medication adherence. MHealth interventions should continue to

be innovated and adopted as helpful tools in improving medication adherence but must be evidence-based and evaluated for their effect on health outcomes.

Dissemination of Research

Peer reviewed publications

1. **Wiecek E**, Torres-Robles A, Cutler RL, Benrimoj SI, Garcia-Cardenas V 2020, 'Impact of a Multicomponent Digital Therapeutic Mobile App on Medication Adherence in Patients with Chronic Conditions: Retrospective Analysis', JMIR, vol. 22, no. 8.

2. Cutler, R.L., Torres-Robles, A, **Wiecek, E**, Drake, B., Van der Linden, N., Benrimoj, S.I.C. & Garcia-Cardenas, V. 2019, 'Pharmacist-led medication non-adherence intervention: reducing the economic burden placed on the Australian health care system', Patient preference and adherence, vol. 13, p. 853.

3. **Wiecek, E**, Tonin, F.S., Torres-Robles, A, Benrimoj, S.I., Fernandez-Llimos, F. & Garcia-Cardenas, V. 2019, 'Temporal effectiveness of interventions to improve medication adherence: A network meta-analysis', PloS one, vol. 14, no. 3, p. e0213432.

4. Torres-Robles, A, **Wiecek, E,** Cutler, R., Drake, B., Benrimoj, S.I., Fernandez-Llimos, F. & Garcia-Cardenas, V. 2019, 'Using Dispensing Data to Evaluate Adherence Implementation Rates in Community Pharmacy', Frontiers in Pharmacology, vol. 10, no. 130.

5. Torres-Robles, A, **Wiecek, E,** Tonin, F.S., Benrimoj, S.I., Fernandez-Llimos, F. & Garcia-Cardenas, V. 2018, 'Comparison of Interventions to Improve Long-Term Medication Adherence Across Different Clinical Conditions: A Systematic Review With Network Meta-Analysis', Frontiers in Pharmacology, vol. 9, no. 1454.

6. Tonin, F.S., **Wiecek, E,** Torres-Robles, A., Pontarolo, R, Benrimoj, S.C.I., Fernandez-Llimos, F. & Garcia-Cardenas, V. 2019, 'An innovative and comprehensive technique to evaluate different measures of medication adherence: The network meta-analysis', Research in Social and Administrative Pharmacy, vol. 15, no. 4, pp. 358-65.

Conference proceedings

1. **Wiecek E**, Torres-Robles A, Cutler RL, Garcia-Cardenas V 2019, 'Gamifying medication adherence: retrospective analysis of a mobile application utilising gamification and incentives to improve adherence', Poster presented at the 23rd Annual International Society for Patient Medication Adherence.

2. Leite J, **Wiecek E,** Torres-Robles A, Cutler RL, Garcia-Cardenas V 2019, 'The effectiveness of using mobile applications to improve medication adherence: a systematic review', Poster presented at the 23rd Annual International Society for Patient Medication Adherence.

3. **Wiecek E,** Torres-Robles A, Cutler RL, Benrimoj, SI, Garcia-Cardenas V 2018, 'Evaluation of a community pharmacy medication adherence service: A study protocol', Poster presented at the 2nd Annual Simpodader Internacional.

4. **Wiecek E**, Benrimoj SI, Fernandez-Llimos F, Tonin FS, Torres Robles A, Garcia-Cardenas A 2018a, 'Comparing the efficacy of intervention strategies to enhance medication adherence: a network meta-analysis', Poster presented at the 1st Annual Pharmacy Practice Research: Postgraduat Students, Postdoctoral Fellows and Supervisors Symposium Conference Organised by the FIP Special Interest Group (SIG) on Pharmacy Practice Research.

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Preface

This thesis is presented in fulfilment of the doctoral degree (Doctor of Philosophy) requirements of the University of Technology Sydney, Australia.

The thesis is structured as a PhD by compilation. Chapter 1 contains a research overview and an outline of the overall rationale, objectives and organisation of the thesis. Chapter 2 provides the background and reasoning for the research. Chapters 3-5 comprise the results including a network meta-analysis assessing comparative effectiveness of interventions to improve medication adherence, evaluation of a mobile health app's impact on medication adherence and an exploration of user beliefs, perceptions and experiences using the aforementioned mobile health app. The chapters have been structured as research articles containing all corresponding references, figures, tables and appendices related to the research activity. This is followed by Chapter 6, which discusses the results, summarises the contribution of work and provides recommendations for future research.

Elyssa K Wiecek is the primary author of each publication. Additionally, co-authors contributed to the conception or design of the work, data collection, data analysis and interpretation, or revision of the manuscripts.

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Abbreviations

ABC Project Team: Ascertaining Barriers for Compliance

ADHD: Attention Deficit Hyperactivity Disorder

AI: artificial intelligence

BCT: Behaviour Change Techniques

BE FIT: The Behavioral Economics Framingham Incentive Trial

CDC: Centre for Disease Control

COREQ: Consolidated Criteria for Reporting Qualitative Research

CrI: Credibility Interval

DIC: Deviance Information Criterion

EMERGE: ESPACOMP Medication Adherence Reporting Guideline

HIV: Human Immunodeficiency Virus

HREC: Human Research Ethics Committee

IQR: Interquartile range

M-DOT: Mobile Direct Observation of Therapy

MAQ: Medication Adherence Questionnaire

MARS: Medication Adherence Report

MEMS: Medication Events Monitoring Systems

mHealth: Mobile Health

MMAS-4: Four-item Morisky Medication Adherence Scale

MMAS-8: Eight-item Morisky Medication Adherence Scale

MPR: Medication Possession Ratio

NICE: National Institute for Health and Care Excellence

OR: Odds Ratio

PDC: Proportion of Days Covered

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO: International Prospective Register of Systematic Reviews

SD: Standard deviation

SOC: Standard of Care

SQL: Structured Query Language

STROBE: STrengthening the Reporting of OBservational Studies in Epidemiology

SUCRA: Surface Under the Cumulative Ranking Curve

WHO: World Health Organization

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Chapter 1

Synopsis

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Rationale

Medication non-adherence is highly prevalent globally with an estimated half of all patient's non-adherent to their medications. Interventions to improve medication adherence have been widely evaluated, including extensive variations in component composition, seeing modest improvements. (Kripalani, Yao & Haynes 2007) A lack of understanding surrounding the effectiveness of individual components within interventions is implicated. (Nieuwlaat et al. 2014) The understanding of the types of effective interventions or their combination of components is essential for the recommendation and feasibility of these interventions within health systems.

Quickly being adapted in the Digital Age is the use of mobile phones to assist in management of health. Widely varying from tools to assist in physical activity to full disease management, mobile health (mHealth) has been quickly adapted by consumers. MHealth facilitates unprecedented connectedness and convenience in a world where approximately 2.5 billion people own a mobile phone. Multiple apps, SMS messages or other novel ways to utilize mobile phones allow for innovative health interventions to be delivered cost-effectively and directly to patients. (Ahmed et al. 2018) Research is struggling to keep up with the fast pace development of these information technologies. While studies have evaluated the effectiveness of some of these tools, evidence is lacking in mHealth interventions aiming to improve medication adherence. The examination of these mHealth interventions adopted by patients is essential for their recommendation by healthcare providers as evidence-based digital health technologies. (Park et al. 2019) The understanding of the beliefs, perceptions and experiences of the users employing them is necessary in their full feasibility as effective and engaging solutions within the health system.

Objectives

The thesis covers the synthesis, analysis and development of knowledge surrounding interventions aimed at improving medication adherence. It evaluated a mHealth intervention in use by Australian patients and provides a holistic overview of evidence with adherence outcomes and user beliefs and experiences. To evaluate interventions aiming to improve medication adherence with a focus on the rise of mHealth, specific objectives were defined:

Specific objectives

- Analyse the comparative effectiveness of interventions for improving medication adherence over time among adults with any clinical condition.
- Assess the impact over time of an implemented mHealth intervention which uses multiple components including rewards, reminders, and education on medication adherence in adults with any clinical condition.
- Explore users' perceptions, beliefs, and experiences of the mHealth intervention by a content analysis of user survey reviews.

Research Overview

Mixed methodologies were used to investigate effective interventions at improving medication adherence with a focus on the adoption of mHealth. Following the overview of the dissertation in Chapter 1, Chapter 2 presents a background to the objectives of the research. The subsequent chapters present a series of works, each addressing a specific objective (Figure 1).

Chapter 3 employs a network meta-analysis to assess comparative effectiveness of interventions to improve medication adherence and their composition of components.

Chapter 4 describes an implemented mHealth app utilising multiple components to enhance adherence to medications. Quantitative analysis using mobile direct observation of therapy (M-DOT) measurements investigates the impact of the intervention on adherence rates over time.

Chapter 5 is a content analysis exploring the beliefs, perceptions and experiences of uses of the evaluated mHealth intervention. Content analyses of user reviews were used to examine the desirability and adoption of the intervention within Australian patients.

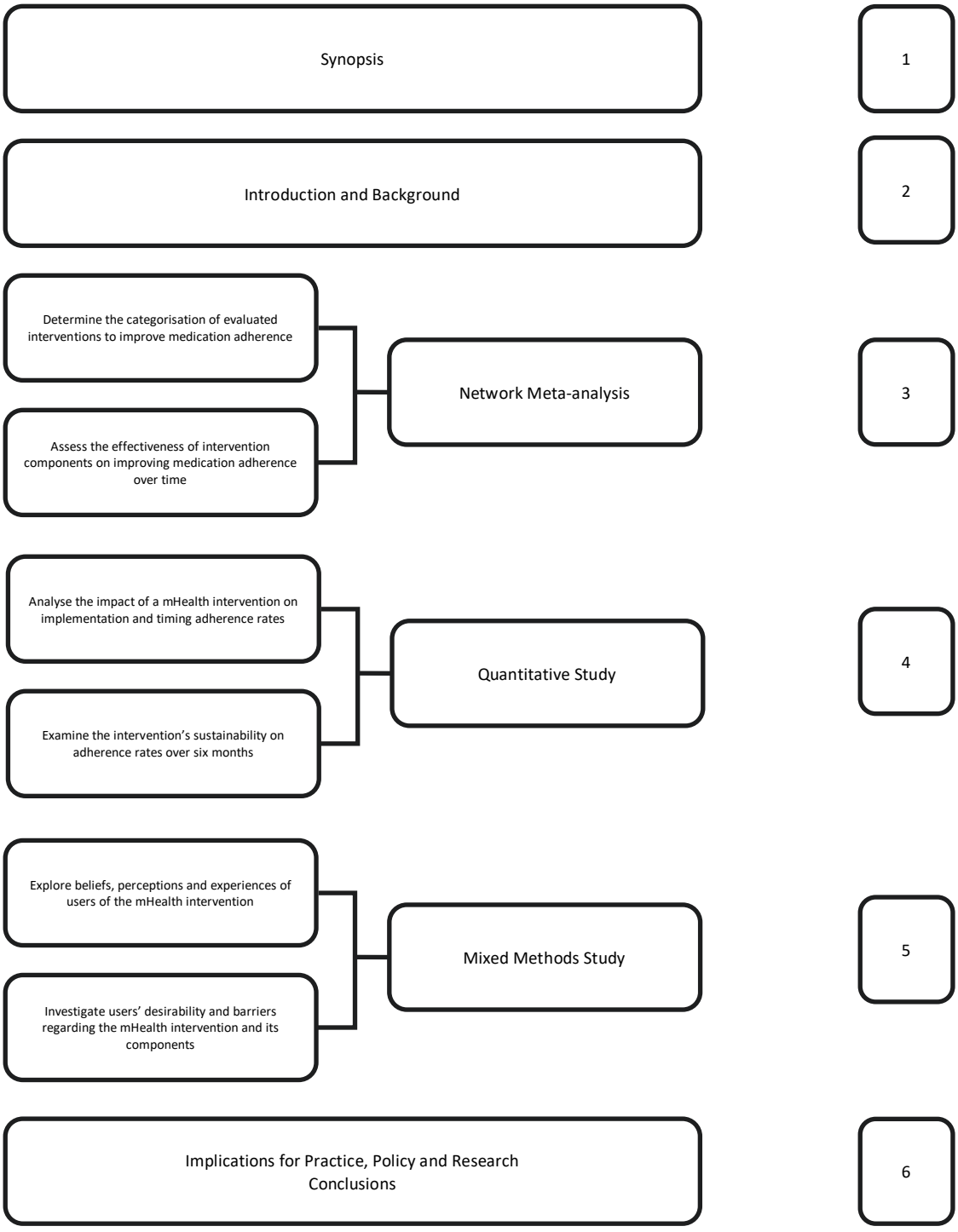

Figure 1. Thesis structure

Temporal Effectiveness of Interventions to Improve Medication Adherence: A Network Meta-analysis (chapter 3)

The first part of the thesis was to review the literature surrounding interventions to improve medication adherence and assess their comparative effectiveness. Multiple systematic reviews and meta-analyses have evaluated interventions either by intervention type or clinical condition, however the literature lacked comparative effectiveness and head-to head evidence of intervention strategies. (Nieuwlaat et al. 2014)

Network meta-analysis is used to compare efficacy among different interventions, rather than just standard care within a traditional pairwise meta-analysis. It allows estimates of relative treatment effects from both direct and indirect evidence to compare interventions to other interventions rather than standard of care alone. (Tonin et al. 2019)

A systematic search of the literature was conducted first for relevant meta-analyses comparing patient-targeted interventions aimed at enhancing medication adherence in adults with any condition. The PubMed search was conducted in January 2019 with no restriction on population, date or language. Primary studies were extracted and included if they reported adherence as an outcome using any measure.

Interventions were categorised within four categories, either singularly or as a combination. Technical components aimed to simplify the medication taking process. Educational components informed on the disease, medication or importance of adherence. Attitudinal components intended to modify beliefs. Reward components created incentives for improved adherence.

The database search identified 1081 meta-analyses with 69 included. A further 1234 primary studies were identified from the meta-analyses with 468 included in the qualitative synthesis and 249 for quantitative synthesis.

The quantitative analysis observed adherence rate follow-ups across four time periods: 0-3 months, 4-6 months, 7-9 months and $\geq$ 10 months. Effective interventions varied across follow-ups of less than 10 months, with significant effects being observed by technical and attitudinal interventions. In follow-ups longer than 10 months, multicomponent interventions displayed the most effective solutions with education in combination with attitudinal and technical interventions showing the highest efficacy. Additionally, reward + technical interventions were found to achieve significant effectiveness, but a lack of evidence (n=1) of the combination prevented concrete conclusions.

The network meta-analysis confirmed, that while non-adherence to medications is a complex issue with multiple dimensions and determinants, multicomponent interventions may be needed to sustain long-term adherence over time. The effectiveness displayed by reward-based interventions but limited by a lack of studies warrants the need to further investigate their potential in enhancing adherence.

The Effects of a Digital Therapeutic Utilizing Gamification and Incentives to Achieve Optimal Medication Adherence: Retrospective Analysis (chapter 4)

The successive part of the research addressed a limitation of the network meta-analysis in that there was a lack of evidence surrounding a comparatively effective intervention component of rewards.

Perx Health is an implemented digital therapeutic, defined as a high-quality software program, in the form of a mHealth app aiming to improve medication adherence. The research assessed their mHealth intervention delivering a combination of rewards, technical, educational and attitudinal components directly to patients. This research aimed to analyse the impact over time of the Perx intervention on medication adherence rates in adults with any condition.

A retrospective observational study was conducted to evaluate adherence rates of users of the Perx intervention. Adherence was measured through mobile direct observation of therapy (M-DOT) over a 3 month and 6 month time period. Implementation adherence was measured and defined as the percentage of doses on which the correct dose of the medication(s) was recorded to have been taken over 30 days at a time. Timing adherence, or percentage of doses recorded to have been taken at the appropriate time (+/- one hour) was also assessed over 30 days at a time.

Three months analysis included 243 users of the app and 130 users were analysed across a 6 month period. The average age of all included users was 43.8 years (SD 15.5) with the most common medications being taken including varenicline, rosuvastatin and cholecalciferol. Over 3 months, implementation adherence averaged at 84.6% (SD 20.9%) and timing adherence at 61.1% (SD 28.5%). For the users observed over 6 months, implementation adherence averaged 87.6% (SD 16.9%) and timing adherence at 68.5% (SD 29.1%).

The assessment of the Perx interventions adds to the evidence that interventions including rewards components can be effective at achieving optimal adherence rates over the standard 80% adherence threshold. The quantitative analysis concluded similarly to the network meta-analysis, that rewards components, especially when in combination with other components can be effective solutions to sustain optimal adherence over time. The results of this research identify an evidence-based mHealth intervention that can be recommended as a tool in assisting in the management of medication adherence.

User Perception of a mHealth Application Using Gamification and Incentives to Improve Medication Adherence: Content Analysis of User Survey Reviews (chapter 5)

The adoption of mHealth tools by consumers and the developing evidence supporting their effectiveness for adherence outcomes demands an investigation of their acceptability, desirability and feasibility within health systems. (Ahmed et al. 2018) To understand the appeal and appreciation of these digital strategies, it is necessary to evaluate the opinions of the users themselves. There is a lack of literature in understanding patient perceptions of mHealth interventions, preventing a full, holistic overview of recommendable interventions to assist in the management of medication adherence.

This research aimed to explore users' perceptions, beliefs and experiences of using the previously evaluated Perx mHealth app that utilised multiple components to enhance adherence including rewards, technical, education and attitudinal components. A retrospective mixed methods content analysis of quantitative and qualitative survey data was used. Users of the Perx app were prompted within one week of starting use of the app and one month thereafter to answer three survey questions including:

1. How likely are you to recommend Perx on a scale from 0 to 10, with 0 being very unlikely and 10 being very likely to recommend?
2. Why did you give Perx that score?
3. What is one thing we could improve within the app?

Quantitative data from question 1 was analysed within Microsoft Excel and qualitative data was assessed in NVivo version 12. Three main coding steps included: (1) initial open coding; (2) establishment of categories, and (3) attraction into themes. Qualitative themes were extracted from patterns found in the content analysis and analysed for frequency.

A total of 6,296 survey responses to the three survey questions were made by a total of 449 Perx users from November 2018 to September 2019. To the question “How likely are you to recommend Perx on a scale from 0 to 10,” 1,026 out of 2,110 responses (48.6%) stated they were very likely (score of 10) to recommend Perx.

Answers to “Why did you give Perx that score?” were mainly positive, with common themes identified in overall positive experiences, a perceived improvement in medication adherence, and appreciation of reminder and reward components. Negative responses related to themes in reward frequency, overall negative experiences, and technological functionality issues.

User answers to “What is the one thing we could improve within the app?” commonly cited the rewards offered, not identifying the intention of frequency or type. Overall positive experiences with nothing to improve were an additional theme as well as the desire for more education and less repetition in disease state and medication facts.

The Perx mHealth intervention is widely accepted by its users with a majority of positive experiences being observed. The appreciation of rewards and reminders, a technical component, were themes identified with negative experiences often encompassing technological functionality issues such as glitches and reward frequency. The overall acceptance and appreciation of the Perx mHealth intervention allows for its recommendation to patients by healthcare professionals.

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Chapter 2

Introduction and background

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Background

The effectiveness of modern medication has allowed for breakthroughs for the human race, from increasing life expectancy to improving quality of life. (World Health Organization 2004) Despite the established effectiveness of evidence-based therapies, adherence to medications remains sub-optimal. (Brown & Bussell 2011) Non-adherence to medication has been shown to lead to worsening health outcomes, increased morbidity and mortality, and increased utilisation of healthcare resources. (Cutler et al. 2019) Medication non-adherence has high prevalence and remains an issue for all countries, developing or developed. Notwithstanding its importance in health and healthcare outcomes, non-adherence is often an overlooked issue of public health and health care systems. (Brown & Bussell 2011; Sabaté & Sabaté 2003) Efforts to understand and combat the prevalence and consequences of medication non-adherence are essential.

Defining medication adherence

Medication adherence has been defined by multiple sources including government institutions, health organisations, and research centres with similar yet differing definitions. ('Enhancing Patient Adherence: Proceedings of the Pinnacle Roundtable Discussion' 2004; Research 2010; Sabaté & Sabaté 2003) Adherence to medications is defined by the WHO (World Health Organisation) as “the extent to which a person’s behaviour – taking medication…corresponds with agreed recommendations from a health care provider.” (Sabaté & Sabaté 2003) Other definitions have underlined that the patient has a choice in taking their medication, one example being, “active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behaviour to produce a therapeutic result.” (Ho, Bryson & Rumsfeld 2009)

Compliance is a term often used interchangeably in the field, defined as "the extent to which a patient acts in accordance with the prescribe interval and dose of a dosing regimen." (Cramer et al. 2008) Compliance is defined differently from adherence in that adherence requires the patient's agreement to the recommendations. Therefore, "adherence" as a term emphasizes that patients should have an active role and collaboration with health professionals regarding their own care and that effective clinical practice stems from a good relationship between doctor and patient. (Haynes 1979; Rand 1993; Sabaté & Sabaté 2003) Additionally, 'patient compliance' over time has adjusted to a negative connotation of patients not "doing as told" or "breaking the rules." (Jimmy & Jose 2011) Compliance and adherence have also been used to describe multiple medical processes including compliance with guidelines, compliance with drug regulations, compliance with appointments, etc. (Cramer et al. 2008) Increasingly adjusting to the term 'medication adherence' allows these confusions and negative connotations to dissolve from the literature.

With four decades of research and thousands of scientific articles on medication adherence, terminology uniformity was lacking. Patient behaviour deviating from prescribed therapies were defined as the same or in many different ways. In 2009, a European consensus meeting using a systematic literature review to establish a new taxonomy which conceptualized and defined different types of medication non-adherence with quantifiable measurement parameters (Vrijens et al. 2012)

"Adherence to medications" is defined as the process by which patients take their medication as prescribed. (Vrijens et al. 2012) The process encompasses multiple behaviours and dimensions that require transparency and replication within their meaning and measurement within the scientific field. The process is further divided into three quantifiable phases: initiation, implementation and discontinuation. Initiation is when the patient takes the first dose of a prescribed medication. Discontinuation occurs when the patient, for whatever reason, stops taking the medication. Finally,

implementation defines the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose. The length of time between the first dose (initiation) and the last dose is defined as persistence. (Vrijens et al. 2012) With this strictly defined terminology, uniformity within the scientific field and presentations allow discussion to advance the field. However, many studies still fail to define which adherence process they are evaluating, creating confusion in measurements and adherence outcomes and an inability to accurately compare adherence results. (Raebel et al. 2013)

Prevalence of non-adherence

The Centre for Disease Control (CDC) states half of adults above age 18 suffer from at least one chronic disease within the United States. (Bauer et al. 2014) In Australia, 47% of adults have one chronic diseases with 20% suffering from two or more. (AIHW, 2018) With chronic disease often comes medication use. Approximately 50% of patients with chronic diseases do not take their medication as prescribed. (Brown & Bussell 2011; Horne et al. 2005; Kleinsinger 2018) While other estimates of adherence rates across clinical trials vary widely, clinical practice ranges are even lower at 10-40%. (Torres-Robles et al. 2019). In the United States, 14-21% of patients with prescription medication fail to fill their original prescription, never reaching the initiation phase of adherence. (Parthasarathi, Nyfort-Hansen & Nahata 2004; Vrijens et al. 2012) Additionally, Australian reports are consistent to the United States with an estimated 41% reporting discontinuation adherence, or having stopped a prescription medication before they were instructed to. (Health & Health 2010)

Reasons for non-adherence

In order to fully understand non-adherence and uncover solutions, the reasons behind non-adherence must be initially identified. While many causes of non-adherence have

been identified, these may fall between two overlapping categories: intentional and unintentional. (Horne et al. 2005; Lehane & McCarthy 2007) Intentional non-adherence happens when the patient makes a decision to not follow treatment recommendations or agreements. This may be based on patients' beliefs and perceptions of treatment as well as motivation influences. Unintentional non-adherence is caused by practical barriers out of a patient's control. Some examples are forgetfulness, not being able to avoid the cost of treatment, or difficulty in understanding the regimen or instructions. (Chapman et al. 2015; Nunes et al. 2009)

It is also important to realise that while the patient may be a contributor to non-adherence, the responsibility of proper use of medication does not lie wholly on them. (Sabaté & Sabaté 2003) Medication adherence remains a challenge in all countries due to numerous reasons related not only to the patient, but also the healthcare system, treatment, condition, and socioeconomic factors. (Sabaté & Sabaté 2003) These factors are interconnected throughout and create the multidimensional model of adherence. (Khan & Socha-Dietrich 2018) Patient factors such as perceptions, beliefs, and motivation add to the equation of non-adherence but do not complete the complex encompassment of non-adherence causes. (Kardas, Lewek & Matyjaszczyk 2013)

Healthcare team and system-related factors

Healthcare team and system-related factors, such as overworked providers or poor medication distribution systems, can affect adherence in both positive and negative ways. Barriers to access of healthcare, and especially high-quality care, are still common in modern society and all countries. Poor access can be exacerbated in rural areas as can long-wait times and queues in healthcare facilities in urban areas. (Sabaté & Sabaté 2003) As the world becomes more globalized as well, we are seeing language barriers in countries with high immigration rates that can aggravate difficulties in accessing

healthcare and medications needed in addition to understanding treatment instructions. (Kardas, Lewek & Matyjaszczyk 2013)

The process of medication-taking is characterized by an interaction between the patient, prescriber, and pharmacist mainly, yet can be impacted by other healthcare and non-healthcare influences such as carers or relatives. Shared decision-making in care plan creation with patients often lead to better adherence results. (Khan & Socha-Dietrich 2018) Often the healthcare systems aim for a patient-centred approach with high communication, yet failure to reach shared decision-making creates a disconnect in a patients' resources and achievement to adherence. Personalisation to the patient and integration of health care professionals are necessary for the approach to understanding the individual patients' health needs and adherence barriers. (Safran et al. 1998) The ongoing process of devising and adapting a customised care plan creates an equal partnership between patient and provider and creates a trusted relationship leading to the ultimate goal of successful health outcomes. (Khan & Socha-Dietrich 2018)

Healthcare team and system-related factors can furthermore lead to unclear or misinformation about a patient's medication taking. Patients are often seeing multiple specialists and health care professionals in order to have a holistic approach to health. However, with non-communicating prescribers, conflicting messages and discrepancies between treatment guidelines are common. (Bosworth et al. 2011) Patients using multiple pharmacies as well can see negative consequences as pharmacy systems may be unable to communicate and therefore could miss dangerous medication interactions or important information about changes in a patient's drug regimen. (Kardas, Lewek & Matyjaszczyk 2013)

Socioeconomic Factors

In addition to healthcare system-related factors, there are socioeconomic factors affecting non-adherence. Examples include low levels of education or socioeconomic status. (Sabaté & Sabaté 2003) Social support and social stigma of a disease, specifically high-profile conditions like HIV (Human Immunodeficiency Virus) status or TB (tuberculosis), can prevent patients from wanting to take their medications in public places. (Rintamaki et al. 2006) The cost of medication and prescription coverage are also becoming major factors of adherence. Unaffordable treatments may cause patients to unwillingly miss doses of their medication needed for positive health outcomes. (Balkrishnan 1998) In countries like the U.S., inadequate prescription coverage and unemployment can cause major gaps in access to medication needed. (Kardas, Lewek & Matyjaszczyk 2013)

In a specific study in New Zealand, prescription costs increased from NZ$3 to $5. While a seemingly low amount, this had a devastating impact on those with lower incomes. Studies on this impact indicated that 6.4% of people reported not picking up a prescription needed due to the cost. In addition, 32.2% of people reporting severe psychological distress. (Norris 2014) The prohibitive increasing costs of healthcare have proven to have a large impact on patients' decisions to take medications and must be a consideration in medication adherence studies.

Socioeconomic factors can also be positive determinants, such as family and social support. A patient living with at least one other person has been shown to increase adherence. (Kardas, Lewek & Matyjaszczyk 2013) Additionally, family cohesiveness and emotional support can have encouraging benefits on a patient's odds of being adherent. Social systems or reminders system, which provide supervision of medication administration and motivational support, can enhance the desire in patients for positive health outcomes. (Amico et al. 2009)

Condition-related Factors

Condition-related factors, for example the severity of the disease and comorbidities, can contribute to patient non-adherence. (Kardas, Lewek & Matyjaszczyk 2013) Obvious physical barriers due to conditions can have an impact, such as being able to swallow a pill safely or not being able to open a pill bottle. The absence of symptoms can also affect non-adherence. Patients that do not feel sick or ill may not believe they require a medication at all or feel the need for daily dosing. (Khan & Socha-Dietrich 2018) These condition-related factors may vary based on the clinical condition of the patient and suggests that interventions addressing these determinants of non-adherence may need to be based on the clinical condition or conditions diagnosed.

Treatment-related Factors

While medications can be an effective solution to improving health outcomes and prolonging life, they can also create unforeseen complications to a patients' daily life. Treatment-related factors are such things such as frequency of doses or side effects. (Kardas, Lewek & Matyjaszczyk 2013) Side effects are often an unavoidable reality for many patients on medications and may deter good adherence. For intentional reasons, patients may avoid a medication they were prescribed if they feel the side effect ruins quality of life. (DiBonaventura et al. 2012)

Moreover, polypharmacy, most commonly defined as taking five or more unique medications, is highly prevalent, especially among older populations. (Masnoon et al. 2017) Within Australia, 36.1% of older Australians aged 70 or more, estimated to be almost one million people, are prescribed five or more unique medications. (Page et al. 2019) Due to the complicated nature of a multiple-medication regimen, patients may have lower adherence. (Kardas, Lewek & Matyjaszczyk 2013).

Patient-related Factors

Patient-related factors affecting adherence encompass a wide range of modifiable and non-modifiable determinants ranging from age or ethnicity to an individual's health beliefs and motivations. (Kardas, Lewek & Matyjaszczyk 2013) It is often found that very old age (older than 85 years) can have a negative effect on adherence. (Kardas, Lewek & Matyjaszczyk 2013) This may be due to lower health literacy or cognitive ability. Patients of Latino, Hispanic or non-white descent are commonly found to have lower adherence rates than Caucasians. (Shenolikar et al. 2006) This is most likely related to another dimension of non-adherence, socioeconomic reasons. Ethnicity may affect socioeconomic status which in turn affects multiple factors such as access to healthcare, family and social support, cost of healthcare or medications, and education or more specifically, health literacy. (Howard, Sentell & Gazmararian 2006)

Additionally, within socioeconomic factors and prohibitive costs of medications ethnicity has correlated with rates of medication adherence. In a US study evaluating medication adherence rates among privately insured patients, average adherence rates among blacks and Hispanics were 7.5% lower than those of their white counterparts. (Xie 2019) While race and ethnicity are complex healthcare topics to unwind based on long histories of colonization, institutional racism, and other largely ingrained system factors that disadvantage certain populations, they remain a major concern in healthcare disparities and a potential target for effective medication adherence interventions.

Education and health literacy play a large role in medication adherence. Those with a higher education level generally have higher adherence levels than those without. Patients with low health literacy may have a more difficult time adhering from not understanding their medication regimen, or by not understanding the benefits of medication and consequences of a disease. (Balkrishnan 1998) Cognitive function as well can have a negative effect on adherence if there is low attention or an impairment.

Frequently, psychiatric conditions are connected with lower rates of adherence and appear to be the only comorbidity to have a correlation. (Kardas, Lewek & Matyjaszczyk 2013)

Similarly related to education, motivation affects all aspects of healthcare and medication adherence. With medications leading to positive health outcomes, a higher quality of life and longevity, (Olsson, Runnamo & Engfeldt 2011) it is difficult to imagine why a patient would not be motivated to correctly take their medications. The same in reverse remains true with the severe and debilitating consequences unmanaged chronic illnesses can cause. Yet, 50% of patients still only remain adherent to their medications worldwide. (Brown & Bussell 2011)

Behavioural economics as a field rejects traditional economics, stating that humans will make rational and logical decisions based on price and information. (Ariely 2009) Alternatively to traditional economics, humans often make irrational decisions based on the context of their environment and emotion that are often hard to predict. This may help explain irrationality around medication adherence decisions.

As an example of irrational decision-making, present bias explains how human tendency leans toward a smaller reward in the present rather than a larger reward in the future. Present-biased preferences explain why humans may reject a behaviour that benefits themselves. Stronger weight and focus remain on earlier moments as they appear closer in time. (O'Donoghue & Rabin 1999) In order to achieve an uncertain and distant benefit, patients have to have certain and immediate inconveniences. Present-biased preferences are commonly seen in students and workers procrastinating, but even more so in health behaviours such as diet and exercise. (Wang & Sloan 2018; Yashkin, Hahn & Sloan 2016) The same applies to medication adherence. The immediate inconvenience of taking a medication can outweigh potential future benefits or consequences from health. Related, theorists have also determined what's known as the peanuts effect.

Humans tend to pay little attention to small but cumulative consequences of repeated decisions. (Loewenstein et al. 2012) This can be seen in small consequences from not taking a medication; slight or even unnoticeable decreases in a patient's health can eventually turn into large consequences such as hospitalizations, costly procedures or even death. (Vik et al. 2006)

In relation to developing effective interventions to improve medication adherence, a problem cannot be solved unless the problem is identified and defined. In order to successfully position strategies to improve medication adherence within healthcare, the causes and determinants of non-adherence must be fully understood. Interventions without this direction may lack the necessary comprehension in how to utilise resources and behavioural strategies to employ. Simultaneously, the understanding that intervention strategies should compensate for individual causes of non-adherence advises that a tailored or multicomponent approach to interventions may be necessary. (Allemann et al. 2016)

Measures of Adherence

Before understanding effectiveness of interventions to improved adherence, measurements of adherence must be defined. Medication adherence has been measured for several decades using numerous different methods. These may vary from subjective strategies, such as self-report, to objective, such as electronic monitoring, with no gold standard. (El Alili et al. 2016) The analysis of methods of measurement is crucial in that the variable or inaccurate measurement of medication adherence can cause dangerous and expensive consequences of misunderstanding evidence. (Lam & Fresco 2015) The accurate measurement and estimation of adherence can provide better scientific evidence. (Lam & Fresco 2015) It is moreover necessary when comparing the effectiveness of different interventions aimed at improving adherence as their method of measurement may affect results. (Garber et al. 2004)

Subjective Measures of Adherence

When adherence was researched in the 1970s, subjective measures were most commonly used. (Lam & Fresco 2015) Subjective measurements include self- or healthcare professional- evaluation of adherence. (Lam & Fresco 2015) A plethora of questionnaires have been developed to measure adherence across multiple disease states, conditions and populations, and to date have been the most common tool used for adherence estimations. (Lam & Fresco 2015) A disadvantage of subjective measures is that patients often tend to overestimate their adherence. This may be a psychological effect of judging one's self or may be due to not wanting to disappoint or be disapproved by a provider, nurse, or pharmacist. (Alcántara et al. 2014; Fleisher & Stern 2013) However, their low cost and ability to also analyse barriers or beliefs about adherence makes them accessible and common. (Lam & Fresco 2015)

Nguyen et al. in a systematic review identified forty-three validated self-report adherence scales, though scales not in English were excluded. (Nguyen, Caze & Cottrell 2014) Generally, most scales focus on implementation adherence rather than initiation and discontinuation phases. Scales can also be different based on what part of the medication-taking process or behaviour they measure.

Three questionnaires of adherence stand out as the most commonly implemented in studies. (Lam & Fresco 2015) The Medication Adherence Questionnaire, or MAQ, is also known as the 4-item Morisky Medication Adherence Scale (MMAS-4). (Morisky, Green & Levine 1986) Identified as the most commonly used and apparent in the literature, the MAQ is the quickest questionnaire to administer and score. A second questionnaire, the Eight-Item Morisky Medication Adherence Scale (MMAS-8) was based on the MAQ and has over time become more popular due to a higher sensitivity and specificity found. (Morisky et al. 2008) In addition to the MAQ, the additional questions focus on

medication-taking behaviours, specifically related to underuse, for example forgetfulness. This is used to evaluate barriers to adherence. (Tan, Patel & Chang 2014) The third questionnaire is the Medication Adherence Report Scale (MARS). MARS also incorporates questions from the MAQ and is therefore able to evaluate both medication-taking behaviours and attitudes and beliefs toward medications with high reliability. (Thompson, Kulkarni & Sergejew 2000)

While these three questionnaires may be commonly utilised and validated methods of measuring adherence, their ability to be compared based on different rating scales creates difficulty in the comparison of adherence measurements between studies.

Objective Measures of Adherence

Electronic measurements of adherence have evolved over the past five decades. (Lam & Fresco 2015) Commonly utilised within packaging devices, electronic measurements have become more popular in recent years and are the closest measurement to a "gold standard". (Anghel, Farcas & Oprean 2019)

Medication Events Monitoring Systems (MEMS) are the most widely known and recognized of the electronic medication packaging devices that records the time a medication container is opened. MEMS is a highly accurate measurement used in several studies and can measure sporadic or consistent medication-taking patterns, as it can detail every day down to the time of dose, therefore identifying partial non-adherence. (Zeller et al. 2008) Drawbacks to MEMS include high costs of such technology and the support required for the equipment and analysis. (Gillespie et al. 2011) Finally, MEMS alone can act as an intervention to improve adherence due to the use reminding the patient they are under surveillance for their medication-taking behaviour. Some MEMS may additionally have reminders. MEMS has been recognised as the reference standard to validate other measures of adherence against since the 1990s. (Lam & Fresco 2015)

Similar to electronic monitoring systems, Mobile Direct Observation of Therapy (M-DOT) has gained more recognition in recent years. (Shields et al. 2018) M-DOT observes the medication-taking behaviour through photos taken of the medication using a mobile device. As traditional Direct Observation of Therapy (DOT) is an expensive and difficult method of measuring adherence with the presence of a trained observer needed for every dose, M-DOT allows a more cost-efficient method utilising common technology from modern everyday life. Additionally, M-DOT can allow doses to be recorded on a time and date, being able to reveal patterns in patient adherence and to measure timing adherence similar to MEMS. Drawbacks to M-DOT, however, include not being able to fully observe if a dose was ingested. However, this limitation may also be present in DOT with patients able to hide tablets under their tongue, and in other methods where patients may always go to great lengths to avoid adherence. (Zullig, Mendys & Bosworth 2017)

Secondary electronic databases include curated primary data in systems, most commonly found in electronic prescription services of insurance claims. Large databases allow the quantification of medication adherence based on refill data. (Blaschke et al. 2012) Due to a patient needing to refill their medication either monthly or tri-monthly, adherence can be estimated by the date in which they pick up their refills or repeats. (Nau 2012) These large databases provide an inexpensive option to analyse adherence rates based on an equation. (Crowe 2013) Two major formulas are commonly used to analyse this data including the Medication Possession Ratio (MPR) and a more conservative measure of Proportion of Days Covered (PDC). Both observe the time between refills using time gaps and medication availability, or days' supply. PDC additionally accounts for surplus supply if a refill is filled early, where MPR does not. (Nau 2012)

$$MPR = (days' supply\ obtained)/(days\ between\ refills)$$

$$PDC = \frac{number\ of\ days\ in\ period\ covered}{number\ of\ days\ in\ period} x\ 100$$

Secondary databases also provide insights into adherence levels of large samples of the population. This data insight facilitates the implementation of pharmacist interventions to improve adherence as the system is able to identify and alert pharmacists if a patient appears to be non-adherent. (Torres-Robles et al. 2019) This method is popular as it allows analysis of large sample sizes providing rapid and cost-efficient results. Many limitations remain with secondary database analysis, including the inability to detect patterns or dates and times of doses taken. (Lam & Fresco 2015). Additionally, patients may receive prescriptions from other sources and are not recorded in a single database. Finally, errors can also range from inaccurate data input to other non-identified switches in medication regimen, pharmacy, or insurance provider, not allowing a full picture of adherence to be established.

With all of these methods of measuring adherence, it is difficult to compare studies utilising different measurements preventing comparative analysis of interventions aimed at improving adherence. Understanding this issue, a validated method within in our network meta-analysis study was created to compare interventions to improve adherence in chapter 3. Networks were created for different types of measurements and analysed, finding enough similarity to be able to be compared. (Tonin et al. 2019) Regardless of being able to compare different methods of measurement of adherence, a lack of a gold standard measurement of adherence remains with positive and negative factors found for all measures and situations.

Clinical Impact of Non-adherence

In order to recognize the need for effective adherence-enhancing interventions, we must understand the consequences of non-adherence. While correct medication use may lead to positive health outcomes, sub-optimal adherence can cause negative clinical effects. Poor medication adherence leads to worsening health outcomes, clinical complications, and even premature death. It is estimated that approximately 200,000 premature deaths were caused due to non- adherence in Europe per annum. (ADD CITATION) In the United States, non-adherence is attributed to 125,000 preventable deaths annually. (Osterberg & Blaschke 2005)

Patients with high adherence on average experience 1.18-5.72 fewer inpatient hospital days compared to patients with low adherence. (Roebuck 2011) Hospitalisation risk is also seen to increase with both diabetes and hypertensive patients with non-adherent patients experiencing 1.5 to 2 times greater risk compared to adherent patients. (Jimmy & Jose 2011; Khan & Socha-Dietrich 2018)

Chronic conditions are particularly susceptible to worsened health outcomes from poor adherence. Patients with diabetes and heart disease who did not adhere to their medications had nearly twice as high mortality rates compared to patients who did adhere. (Brown & Bussell 2011; Cramer 2004; Khan & Socha-Dietrich 2018) Additionally in heart disease, patients who discontinued their statin therapy before agreed upon faced a three times higher risk of heart attack. (Khan & Socha-Dietrich 2018; Maningat, Gordon & Breslow 2013) Non-adherence to beta-blocker therapy causes a 4.5 times higher risk to have complications from coronary heart disease compared to adherent patients. (Cramer et al. 2008)

Indubitably, the clinical impact of non-adherence is exceedingly significant on patient health outcomes. While the development of more efficacious medications is warranted, the improvement of medication adherence could potentially impact positive patient

health outcomes more drastically. (Tanna & Lawson 2016) It is therefore crucial to investigate strategies and solutions aimed to improve medication adherence.

Current Interventions to Improve Medication Adherence

A wide array of interventions to improve medication adherence have been developed and tested in the literature over the past five decades. (Kripalani, Yao & Haynes 2007) Across multiple settings, populations and clinical conditions, interventions have shown marginal success in improving adherence and health outcomes. These interventions range from simple, single component strategies such as an educational pamphlet, to complex, multicomponent interventions incorporating multiple healthcare professionals and resources. (Nieuwlaat et al. 2014) Though many interventions may be directed at others such as healthcare professionals, the majority of interventions are specifically delivered to the patients. Interventions and their components can be categorised into four overarching categories: educational, attitudinal, technical and rewards. (Wiecek et al. 2019)

Educational components of interventions aim to inform patients on the medication, clinical condition, or importance of adherence. Having been most commonly used, educational interventions may include simple written information delivered directly to a patient or more complex, educational sessions delivered continuously and verbally by a healthcare professional. (Sapkota et al. 2015) Modern times have witnessed the increase of digital tools as an innovative method to deliver information, yet the pharmacist remains a commonly utilised position to deliver medication information to patients at the time of dispensing. (Cutler et al. 2019; Presley, Groot & Pavlova 2019)

Attitudinal interventions aim to modify beliefs of a patient towards their health or medication use. These components are often used when a patient may be intentionally non-adherent. Motivational interviewing is the most commonly utilised attitudinal

technique to encourage adherence to medications and requires in-depth training of healthcare professionals delivering these methods. (Wiecek et al. 2019)

Technical components of interventions to improve adherence intend to simplify the medication-taking process. These components often include dosage reminders, pill boxes, electronic feedback, or regimen simplification and often act on unintentional determinants of non-adherence. (Wiecek et al. 2019)

Reward components create incentives for better medication adherence. Rewards are generally of monetary value, either through cash or savings in medication costs, or may be employed in a lottery-based system to encourage adherence. Incentive-type intervention components are not as common as the other categories within the adherence literature but can often be seen commonly in other aspects of public health policy. (Wiecek et al. 2019)

Interventions to improve medication adherence have seen modest results in varying forms and strategies. (Nieuwlaat et al. 2014) As importantly discussed in the background, reasons and determinants of non-adherence are vital for understanding which specific approaches will work best for a patient. Though unfortunately not often utilised and difficult to implement, personalised approaches based on a patient's specific, individualised barriers to adherence may be the ultimate intervention. (Allemann et al. 2016) An example of approaches based on these barriers identified in the WHO Five Dimensions of Adherence and intentional vs unintentional non-adherence can be seen in Figure 2, though this is not a definitive list.

Observing incidence of barriers and by using multicomponent approaches, we can target multiple barriers to non-adherence within one intervention. Unfortunately, the evaluation of individual component within these "package" type interventions with multiple components is not reported. (Costa et al. 2015) Therefore, it is difficult to

estimate if all components are necessary for the enhancement of adherence, if some can be dismissed to reduce cost and resources needed to deliver the intervention, or if a specific combination of components has significantly higher effectiveness.

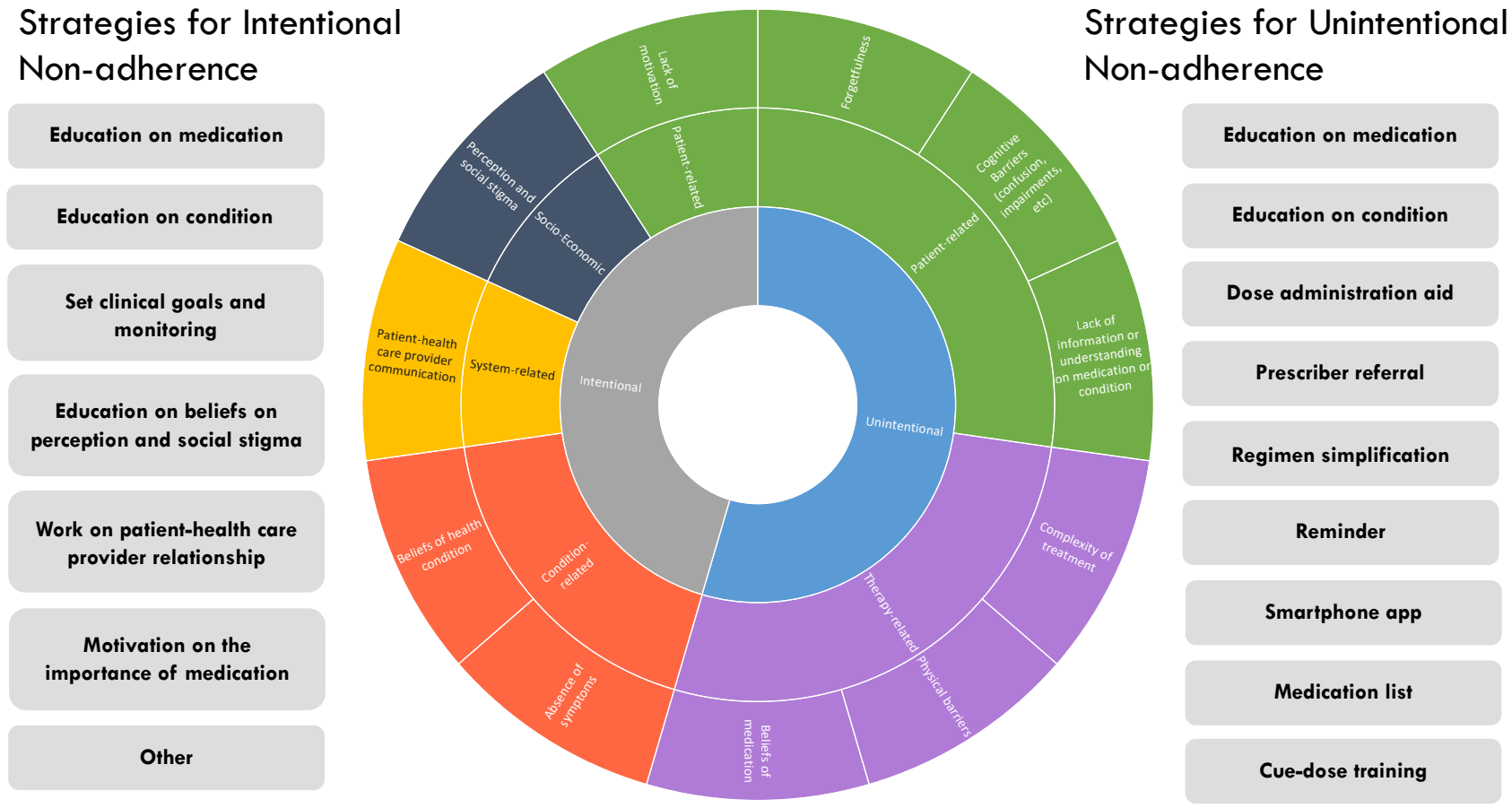

Figure 2. Intervention strategies based on barriers to adherence

Mobile Applications to Improve Medication Adherence

The expansion and adoption of modern technology such as mobile phones has created innovative methods to change health behaviour. MHealth, or mobile health, meaning the practice of medicine and public health supported by mobile devices, provides numerous opportunities to change health behaviours such as weight loss, diet, and disease management. (Ahmed et al. 2018) With an estimated two billion smartphone users known, there have been 3.7 billion downloads of mHealth apps in 2017. (Ahmed et al. 2018; Bhih, Johnson & Randles 2016; Research2Guidance 2017)

Many apps aimed at improving adherence are available for download in consumer markets yet the literature on the effectiveness and acceptability of these strategies remains minimal. A recent systematic review was conducted in 2019 that identified experimental studies evaluating a mobile or tablet application aimed at improving medication adherence in any age group for any clinical condition. From 1,551 potential articles retrieved, twelve studies were included in the review. (Leite et al. 2020)

Commonly utilised within mHealth, medication dosage reminders are a simple tool, evolved from basic reminder systems of the past and were the most common technical intervention component identified in our review in chapter 3. Medication reminders have long been utilized and declared an effective intervention to improve non-adherence due to unintentional reasons like forgetfulness. (Fenerty et al. 2012) In the systematic review of mHealth apps, most apps included a simple interface to alert patients when a dose of their medication was due. Seen in Mohan et al., dose reminders improved adherence from baseline to six months when implemented and evaluated on 100 patients with asthma. (Mohan et al. 2018) Reminders were able to be personalized and customized by patients for their convenience. Compared to a control group using reminder cards to improve adherence, adherence was increased in the intervention group by a mean difference of 5.02 (p=.001) measured by the MMAS-8 self-reporting

scale. In a different population of 39 children diagnosed with attention deficit hyperactivity disorder (ADHD), medication dosage reminders only slightly improved adherence compared to the control group. (Schonherz et al. 2018) This may be due to multiple reasons, one being different populations, such as children, may not find reminders as helpful.

Educational interventions have been standard place in strategies to improve medication adherence for decades. (Nieuwlaat et al. 2014) Mobile apps have given the ability to transfer information to patients through an easy and convenient method, rather than having a trained healthcare professional deliver information. Mobile technology can also allow education to be delivered in an engaging and entertaining manner. Found in the systematic review, eight apps incorporated some type of educational component including material about a condition, medication treatment instructions, clinical outcomes or treatment goals. In a comparison of two different mobile applications, one included an educational component on the patients' condition and treatment while the other did not. The group using the advanced app with education had significantly higher average adherence as measured by the MARS 9 item scale (p=.03). This is attributed within the study to patients within this group gaining a greater and appreciable perception of the need for the medication. (Perera et al. 2014)

MHealth interventions have also created an opportunity for patients to be able to easily communicate with peers, pharmacists or physicians and are often utilised as attitudinal interventions to motivate patients. Morawski et al analysed the impact of a mobile app that allowed patient adherence data to be available to a close friend. The aim of this strategy was for a friend to motivate a patient with hypertension to be adherent. Compared to a standard care control group, adherence was significantly improved in the intervention group. (Morawski et al. 2018) Contreras et al evaluated a mobile app that included a chat function with physicians. The physician could provide advice, motivation and training to patients when needed, acting as an educational and attitudinal

intervention. The intervention group had 86.3% adherence after 12 months compared to an average adherence rate of 62.66% in a control group. (Márquez Contreras et al. 2019) Other communication components seen in mobile apps to include adherence was an alert to either a healthcare professional or caregiver if a patient missed a dose. Labovitz et al assessed a strategy that alerted clinic staff in real time when a dose was missed, taken late, or based on incorrect usage which provided an opportunity to intervene when necessary that was found effective. (Labovitz et al. 2017) Finally, an app including a peer and pharmacist chat function was also found to be effective in a study by Kosse et al. This allowed the pharmacist to monitor outcomes and to either facilitate contact or send additional educational material. (Kosse et al. 2019a)

Symptom or clinical outcome monitoring, considered technical interventions, have been commonplace in adherence interventions in the past but are often recorded by a healthcare professional. The introduction of mobile technology allows a patient to enter symptoms or outcomes and deliver them to a healthcare professional in real time for evaluation. An app evaluated by Kleinman et al included clinical outcome monitoring as a primary measure. Patients with type 2 diabetes mellitus were reminded to complete daily tasks such as medication taking and recording blood glucose levels. If blood glucose was determined to be out of standard range, the app generated an automated follow up questionnaire to identify potential underlying reasons. As determined by patient self-report, adherence to medications was improved compared to a standard care group at a 6 month follow up. (Kleinman et al. 2017)

Outside of medication adherence but within the emerging mHealth field, innovative motivators have been employed for various positive health behaviour changes. Gamification is the “application of game elements for purposes other than their expected use for entertainment.” (Dicheva et al. 2015) Game elements, such as points systems or daily streaks, have high potential to drive intrinsic motivation in addition to engagement that can facilitate positive health behaviour changes. (Ahmed et al. 2015;

Miller, Cafazzo & Seto 2014) Revealed to be effective in multiple health behaviour changes such as smoking cessation or increased physical activity, gamification is still an unfamiliar strategy in managing medication adherence that warrants further exploration. (Patel et al. 2017; Pløhn & Aalberg 2015)

MHealth, including mobile apps and digital health technologies aiming to improve medication adherence, hold multiple advantages in their adaptability and ease of personalisation. Though mHealth may vary from multiple strategies to change patient behaviour, their effectiveness has been proven within medication adherence and justifies further evaluation of these quickly developing and innovative interventions. (Leite et al. 2020) While many components of mHealth apps, such as technical components (i.e. reminders), educational and attitudinal components have been researched, other strategies such as rewards and gamification concepts have yet to be evaluated. It is warranted that any mHealth intervention being utilised on a consumer market should be evaluated for its effectiveness on adherence and health outcomes. Furthermore, mHealth interventions will need to be evaluated within different populations to understand their full potential in improving adherence.

User Perceptions

After evaluating the effectiveness of mHealth interventions, it appears fast adoption of these strategies by consumers has left a gap in the research of understanding of user beliefs, perceptions and experiences surrounding mHealth. Few analyses have identified and evaluated public reviews of mHealth apps as well as qualitative studies using focus groups or questionnaires have evaluated users' of mHealth apps opinions. (Park et al. 2019; Vo, Auroy & Sarradon-Eck 2019) While research has concluded mHealth apps are viewed by users as a useful tool in managing many aspects of health, patient opinion on specific medication adherence enhancing apps, as well as specific components of app most utilised, are lacking.

User experience (UX), or the reflection of user's perceptions and attitudes about using a particular product, informs a crucial element of mHealth intervention design that can strongly affect the impact of a mobile intervention on patient outcomes. Poor user experience design can lead to low levels of engagement, poor understanding of how to use the intervention, or low adoption of the intervention by both patient consumers and other stakeholders. The measure of usability, or how easy and efficient is it to use the app, is often measured by multiple instruments to better understand the end user experience and the product's potential for high uptake and engagement. The three most common scales for usability testing include System Usability Scale (SUS), the Single Ease Questionnaire (SEQ), and the NASA (National Aeronautics and Space Administration) Task Load Index (NASA-TLX).

Potential for further research of the Perx intervention should include formal usability and user experience testing. While UX design methods and continuous testing were used in the development of the Perx mobile app, a formal and unbiased review from a separate party could benefit the knowledge on the uptake and potential for impact and engagement of the Perx intervention in chronic disease patients. The System Usability Scale (SUS) would be an informative questionnaire to further understand a patient's understanding of the app functions as well as the ease of use of the intervention without further support or training. Furthermore, the Mobile App Rating Scale (MARS) could be applied to evaluate the quality of engagement, functionality, asthetics and information within the Perx mobile app. (Stoyanov et al. 2015)

It is crucial not only to assess effectiveness of these mHealth tools but to understand their acceptability, areas of improvement as identified by its users, and their feasibility of integration and patient engagement. (Amico et al. 2009; Vo, Auroy & Sarradon-Eck 2019) Qualitative and mixed methods studies using content analysis are a useful method

of understanding a full overview of user opinions within their own experiences and offer beneficial insight in how to improve these tools for a better user engagement and effectiveness in improving adherence or health outcomes.

Implications of medication non-adherence and mHealth

Sub-optimal levels of adherence and health outcomes with a growing and aging global population and increased rates of chronic disease and comorbidities are a challenge for the health care systems. The magnitude of non-adherence and potential consequences warrant in-depth research into methods and solutions for improving adherence to medications. While the literature has often addressed multicomponent interventions as the most effective strategy moving forward as well as the potential of mHealth avenues, major gaps remain within the adherence landscape that require further investigation.

1. *What components or combination of components make up the most effective adherence enhancing interventions within the current literature?*
2. *What is the impact of utilising these components within a mHealth intervention?*
3. *What are the beliefs, perceptions and experiences of users towards a mHealth intervention encompassing these components?*

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Chapter 3

Temporal effectiveness of interventions to improve medication adherence: A network meta-analysis

Wiecek, E, Tonin, F.S., Torres-Robles, A, Benrimoj, S.I., Fernandez-Llimos, F. & Garcia-Cardenas, V. 2019, 'Temporal effectiveness of interventions to improve medication adherence: A network meta-analysis', PloS one, vol. 14, no. 3, p. e0213432.

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0213432

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Abstract

Introduction

Adherence-enhancing interventions have been assessed in the literature, however heterogeneity and conflicting findings have prohibited a consensus on the most effective approach to maintain adherence over time. With the ageing population and growth of chronic conditions, evaluation of sustainable strategies to improve and maintain medication adherence long term is paramount. We aimed to determine the comparative effectiveness of interventions for improving medication adherence over time among adults with any clinical condition.

Materials and methods

Meta-analyses evaluating interventions to improve medication adherence were searched in PubMed in January 2019 and reviewed for primary studies. Experimental studies with a comparison group assessing an intervention to enhance medication adherence in adult patients with reported adherence outcomes were included. Two authors extracted data for study characteristics, interventions and adherence outcomes. Interventions were categorized into four groups or combinations: educational, attitudinal, technical and rewards. Four network meta-analyses were performed to compare interventions based on patient follow-up time. Medication adherence effect sizes were reported as odds ratios (OR) with a 95% credibility interval (CrI) and surface under the cumulative ranking curve (SUCRA) to allow ranking probabilities. Risk of bias was assessed as per Cochrane guidelines.

Results

Data was obtained from 69 meta-analyses with 468 primary studies being included in qualitative synthesis. The four networks compromised of 249 studies in total (0-3 month follow-up: 99 studies, 4-6 months: 104, 7-9 months: 18, ≥10 months: 94). Interventions showing success in follow-ups of less than 10 months varied across time. Significant effects compared to standard of care (SOC) were found in technical (4-6 months: OR 0.34, 95% CrI 0.25-0.45) and attitudinal interventions (7-9 months: 0.37, 0.17-0.84). Multicomponent interventions demonstrated effectiveness compared to standard of

care with an additive effect displayed, particularly in longer follow-ups (educational + attitudinal + technical interventions ≥10 months: OR 0.49, 95% CrI 0.27-0.88).

Discussion

All interventions reviewed improved medication adherence compared to standard of care. Multicomponent interventions displayed the most promising results in maintenance of long-term medication adherence. Technical and reward components enhanced adherence on a short-term basis, while educational and attitudinal interventions evolved over time to be more effective in follow-ups greater than 7 months. Sustainability of adherence to medications over time is dependent upon multicomponent interventions including educational, attitudinal and technical aspects to modify and enhance patient medication-taking behavior. Future research should focus on the most cost-effective approaches able to be integrated into routine practice.

Introduction

A significant proportion of health care system funding is spent on medications, with 10% of U.S. national health expenditure attributed to prescription medications in 2016 [1]. As only 50% of patients reportedly take their medications as prescribed, medication non-adherence is a major challenge for the health care system [2]. Suboptimal adherence to prescribed medications not only increases health care costs but also increases the possibility of poor health outcomes, adverse events and hospitalizations [3, 4]. It is estimated that failure to adhere to medications results in $290 billion per year in unnecessary expenditure in the U.S. [5].

Adherence is not simply a matter of patient choice or will [6-10], but is affected by the interplay of multiple determinants of adherence that the World Health Organization (WHO) has classified into five different dimensions – condition-related factors, therapy-related factors, patient-related factors, socio-economic factors and healthcare team and system-related factors. While patient population characteristics may have an effect on adherence, determinants and barriers for non-adherence are often comparable across different medications and clinical conditions. [11-13].

Medication adherence can be conceptualized as having three major components: (1) initiation – when the patient takes the first dose of a prescribed medication; (2) implementation – the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen from initiation until the last dose is taken, and (3) persistence – the time from initiation to discontinuation [14]. Non-adherence can occur in any of these phases, and may change over time in patients. There is substantive evidence of a declining trend in adherence over time [15-18], and many determinants of non-adherence are found to be affected by time [6]. Time-related factors are particularly important for people with chronic diseases, where lifetime adherence to therapy may be required.

Numerous multifaceted adherence-enhancing interventions, ranging from simple educational material to multicomponent approaches integrating advanced behavioral

and educational techniques, have been proposed and tested in a wide variety of settings, populations and clinical conditions, using a wide range of measures of adherence [11, 19, 20]. Recent meta-analyses have not reached a decisive conclusion, with some suggesting cognitive-educational interventions are effective [21] and others promoting habit-based strategies [19]. A Cochrane systematic review also concluded interventions' effects were inconsistent across studies, however, they found the most effective interventions to be complex with frequent patient interaction [11]. Unfortunately there is additionally a lack of direct, head-to-head evidence of intervention strategies and combined with the complexity of the literature, makes it a challenge to select evidence-based interventions for implementation in routine clinical practice.

Network meta-analysis is a technique recommended by the International Society for Pharmacoeconomics and Outcome Research to compare efficacy among different interventions [22]. Compared with pairwise meta-analyses, it provides robust comparative evidence, allowing for estimates of relative treatment effects on both direct and indirect evidence [23]. This approach to evaluate all treatment options to each other simultaneously allows more optimal guidance on comparing interventions to other interventions rather than the common comparator of standard of care alone.

The aim of this systematic review and network meta-analysis was to analyze the comparative effectiveness of interventions for improving medication adherence over time among adults with any clinical condition.

Materials and methods

The PRISMA extension to network meta-analysis and Cochrane Collaboration recommendations to design and report were used for this systematic review and network meta-analysis [24-26]. The review is registered on PROSPERO at CRD42018054598.

Data sources

A systematic search of the medical literature was conducted for relevant meta-analyses comparing patient-targeted interventions to improve medication adherence in adult populations reporting adherence outcomes. The search was conducted on PubMed in January 2019 without any restriction based on publication date or language. The complete search strategy is available in S1 Table. Two investigators (EW, ATR) independently reviewed all abstracts and full-text articles and discrepancies were solved by a third reviewer. The primary studies included in the meta-analyses were then fully reviewed.

Study selection

Primary experimental design studies with a comparison group that assessed an intervention with the objective of improving medication adherence in adult patients and which reported implementation adherence as an outcome using any measure (e.g. self-report, pill count, electronic monitoring) were included. Other active interventions or standard of care were considered as comparators. Unpublished studies, articles written in non-Roman characters, with pediatric populations (<18 years), assessing interventions targeted at healthcare professionals or studies using other types of treatment (over-the-counter medications, depot medications, vaccines) were excluded. Studies were not restricted by country, clinical condition or trial follow-up. Eligible primary studies with categorical medication adherence outcomes (i.e. adherent vs non-adherent) were included in the network meta-analyses while those with continuous outcomes were only included in the qualitative analysis.

Data extraction and quality assessment

The following data from primary articles was extracted by two investigators (EW, ATR) using a standard data sheet piloted with 28 studies: study baseline characteristics (authors, year, title, sample size, clinical condition, demographics, duration of study, evaluated interventions), study design, measure of adherence used, variable type (continuous versus categorical) and corresponding adherence rates before and after the intervention.

To standardize the results obtained from different measures of adherence, an overall composite adherence outcome was used for categorical variables that represented the rate of adherent patients obtained from any of the measures in each study. The overall composite score was validated by Tonin et al, 2018 [27]. If a study included more than one measure, a mean rate from the different measures of adherence was calculated.

According to the patient follow-up period of each included study, results were grouped based on patient follow-up and results of adherence reported into standardized periods of time: 0-3 months, 4-6 months, 7-9 months, and ≥ 10 months.

To improve interpretability, interventions were grouped into four categories: attitudinal components aiming to modify beliefs, reward components creating incentives, educational components to inform on the medication, disease state, or importance of adherence, and technical components intended to simplify the medication taking process. The development and categorization process was discussed in Tonin et al, 2018 [27], and full category definitions can be found in S2 Table. Multicomponent interventions included more than one single category (e.g. rewards + technical). Standard of care was considered as the usual care defined in the primary study.

Two reviewers (EW, ATR) assessed all articles using the Cochrane Risk of Bias tool [28]. Given the complexity of interventions and to avoid a floor effect, adjusted criteria for judgement of risk of bias were used. The adjusted criteria allowed for low risk of bias indicated if outcomes were not blinded but were measured with validated instruments (i.e. previously validated medication adherence questionnaires).

Data analysis

Network meta-analysis was performed using Bayesian framework to analyze the comparative adherence of all the interventions for the overall composite measure of categorical measures in each time period. Interventions were modelled as they were described in the original studies, that is, as different combinations of components. Only implementation adherence outcomes could be used for comparison purposes. For all comparisons, a common heterogeneity parameter was assumed, and a conservative analysis of non-informative priors was chosen [29, 30]. Effect sizes measures were

expressed as odds ratio (OR) with a 95% credibility interval (CrI). Heterogeneity between trial comparisons was estimated by using the I^2 statistic. Both random and fixed effect models were tested. The goodness of fit of the model was assessed using residual deviances (DIC). Models with lowest DIC were used**.** Convergence was attained based on visual inspection of Brooks-Gelman-Rubin plots and potential scale reduction factor - PSRF ($1<PSRF\leq1.05$) [30, 31]. To increase the estimate precision of the relative effect sizes of comparisons and to account properly for correlations between multi-arm trials, rank probabilities involving all the interventions were built for each outcome. The surface under the cumulative ranking curve (SUCRA) analysis was performed to present results of ranking order. SUCRA values can range from 0% (i.e. the intervention always ranks last) to 100% (i.e. the intervention always ranks first) [32]. Node-splitting analyses were used to assess inconsistency in the networks (p-values<0.05 reveal significant inconsistencies in the network) [33]. All analyses were performed using software Addis version 1.17.6 [34]. Other sensitivity analyses with the hypothetical removal or inclusion of the studies were conducted based on article's year of publication (before or after 2007) and sample size (total number of included patients over 30).

Results

Database searching identified 1081 records. Sixty-nine meta-analyses were included for primary study extraction. From these, 1234 primary studies were identified and 468 studies were included for qualitative synthesis (see Fig 1) (S1 Appendix). The most common single interventions were educational (n=172 studies), followed by technical (n=118), attitudinal (n=57) and rewards (n=2). Combinations of two or more categories of interventions were found in 191 trials (41.0%) with most of them reporting educational + technical (n=94), educational + attitudinal (n=62) and educational + attitudinal + technical (n=25). Standard of care was the common comparator in 88.0% of studies. The earliest studies were published in 1971 and the most recent in 2017

(median=2008; IQR 2002-2012). Twelve clinical conditions were included with the most common being cardiovascular (n=206 studies) and HIV (n=96).

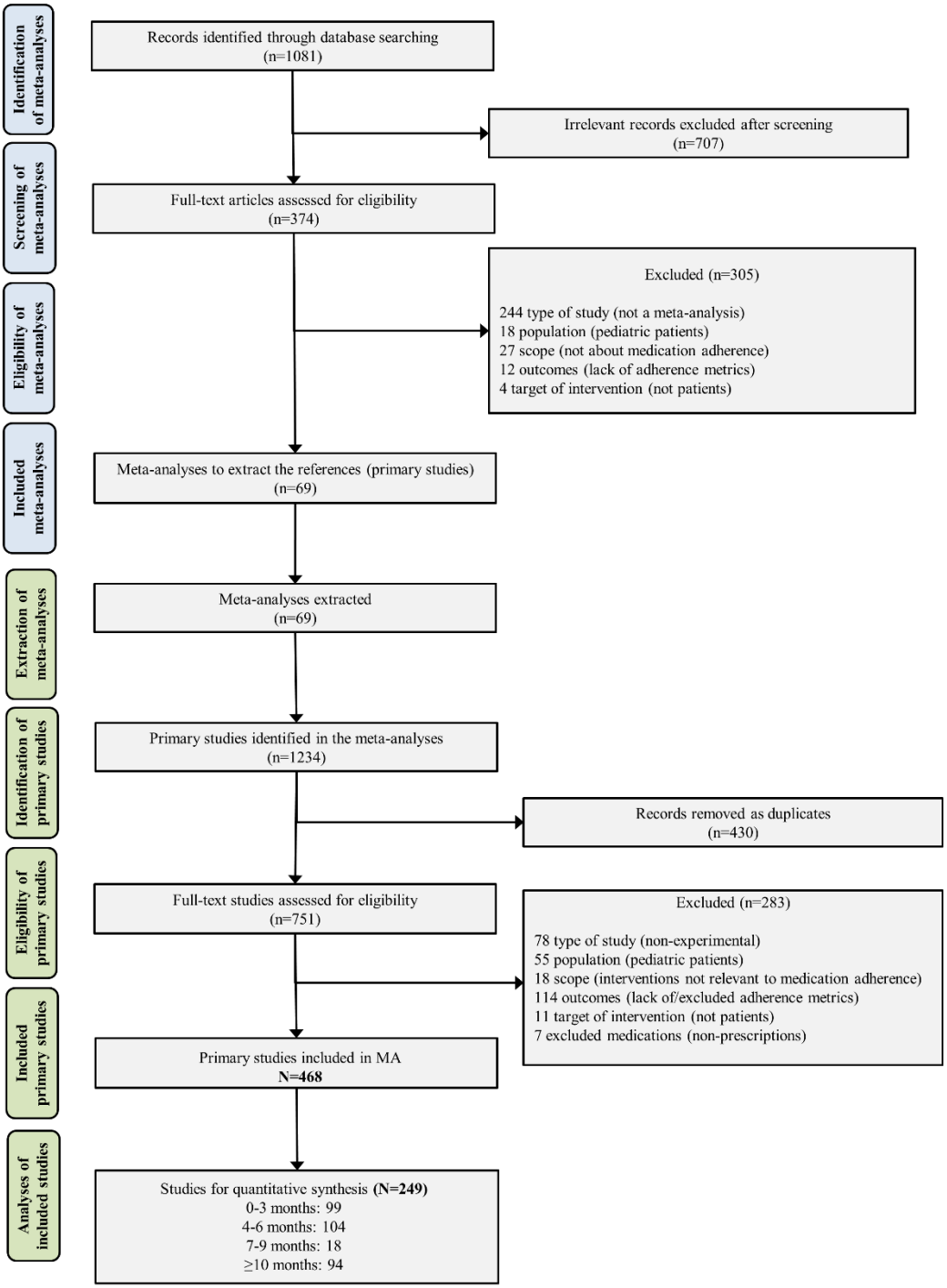

Fig 1. Flowchart of the systematic review process and included studies

Risk of bias assessment revealed most studies having an unclear risk of bias. The domains with higher risk of bias were attrition bias (around 25% of studies) and performance bias (30% of studies) as studies lacked complete outcome data or were unable to blind participants due to the nature of the interventions. More than 90% of studies were free of selective reporting. Fewer than 10% of trials were sponsored by industries or presented conflict of interest (S1 Fig and S3 Table).

For the quantitative network analyses, 219 studies were excluded due to the absence of categorical data on patient's adherence. Another 11 trials were excluded as intervention arms were grouped in the same category and were unable to be compared in the network (e.g. technical vs. technical). Finally, 249 studies were included in the network meta-analyses of overall composite measure for the four periods of time with studies able to be included in more than one time period: 99 studies reporting results in the 0-3 month follow-ups, 104 in the 4-6 months, 18 in 7-9 months, 94 in ≥10 months. Seventy-one studies reported in more than one time period. Six interventions, in addition to standard of care, were evaluated in all the four time periods: attitudinal, educational, educational + attitudinal, educational + attitudinal + technical, educational + technical, and technical. The network plots of each time period with nodes representing the interventions are presented in Fig 2. Heterogeneity between trials for the composite measure analysis was moderate for the majority of the comparisons (81.3% $I^2 < 70\%$) (S4 Table).

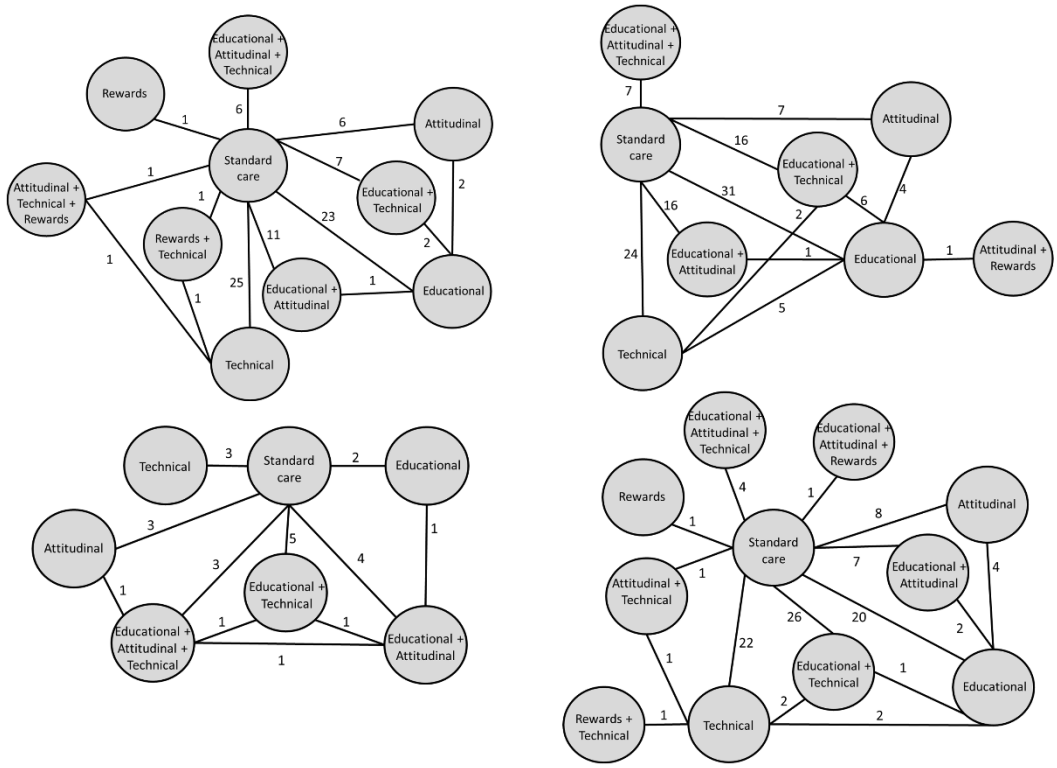

Fig 2. Networks of the comparisons between interventions for each time period (0-3 months, 4-6 months, 7-9 months, ≥10 months) considering the overall composite measure of adherence. Each node represents an intervention. Directly comparable interventions are linked with a line, the number of trials for each comparison are shown in each line.

From the 16 built networks, accounting for both original and sensitivity analyses, 107 nodes were split during the evaluation of inconsistency (node-splitting analyses). Overall, results of direct and indirect evidence were consistent for all these networks (p-values > 0.050 in all cases), suggesting that conditions required for the analyses were met. Only 7 comparisons presented p-values close to the limit of significance (between 0.050 and 0.070). For complete results of node-splitting analyses are presented in S5 Table. The effect size of all the comparisons between interventions in each time period is presented in Table 1. The ranking probabilities of each intervention to be the best, second best and so on is expressed as SUCRA analysis (Fig 3 and S2 Fig).

Table 1. Consistency analyses of multiple comparison analyses for the overall composite measure in part A: 0-3 months (top right) and 4-6 months (top left) and part B: 7-9 months (bottom right) and ≥10 months (bottom left).

A											
Att + Rew	--	--	--	--	--	--	--	--	--	--	--
--	Att + Tec + Rew	1.28 (0.11, 13.70)	0.48 (0.07. 2.64)	2.94 (0.29, 26.39)	1.67 (0.08, 108.62)	0.38 (0.05, 2.26)	0.48 (0.07, 2.60)	0.57 (0.08, 3.24)	0.42 (0.06, 2.19)	0.25 (0.04, 1.31)	0.46 (0.07, 2.48)
--	--	Att + Tec	0.37 (0.08, 1.80)	2.27 (0.27, 19.61)	1.31 (0.07, 84.69)	0.28 (0.05, 1.62)	0.37 (0.07, 1.94)	0.44 (0.08, 2.48)	0.32 (0.06, 1.67)	0.19 (0.04, 1.01)	0.35 (0.06, 1.91)
0.90 (0.19, 4.46)	--	--	Att	**6.40 (1.60, 26.69)**	3.60 (0.30, 103.50)	0.72 (0.36, 1.43)	0.93 (0.53, 1.66)	1.23 (0.62, 2.34)	0.91 (0.56, 1.47)	**0.54 (0.35, 0.85)**	0.99 (0.60, 1.65)
--	--	--	--	Rew + Tec	0.57 (0.03, 20.93)	**0.11 (0.03, 0.47)**	**0.15 (0.04, 0.58)**	**0.19 (0.05, 0.79)**	**0.14 (0.04, 0.55)**	**0.09 (0.02, 0.32)**	**0.16 (0.04, 0.58)**
--	--	--	--	--	Rew	0.20 (0.01, 2.51)	0.26 (0.01, 3.18)	0.34 (0.01, 4.00)	0.26 (0.01, 3.00)	0.15 (0.01, 1.76)	0.28 (0.01, 3.28)
0.55 (0.11, 2.76)	--	--	0.61 (0.30, 1.25)	--	--	Edu + Att + Tec	1.30 (0.67, 2.57)	1.70 (0.81, 3.58)	1.27 (0.69, 2.33)	0.75 (0.43, 1.32)	1.38 (0.74, 2.55)
0.68 (0.14, 3.27)	--	--	0.75 (0.40, 1.38)	--	--	1.23 (0.65, 2.28)	Edu + Att	1.31 (0.71, 2.38)	0.97 (0.64, 1.48)	**0.58 (0.40, 0.83)**	1.06 (0.68, 1.64)
0.78 (0.17, 3.72)	--	--	0.85 (0.47, 1.57)	--	--	1.41 (0.77, 2.64)	1.14 (0.70, 1.88)	Edu + Tec	0.75 (0.43, 1.27)	**0.45 (0.27, 0.73)**	0.81 (0.45, 1.43)
0.65 (0.15, 2.94)	--	--	0.72 (0.42, 1.20)	--	--	1.18 (0.67, 2.08)	0.96 (0.62, 1.49)	0.84 (0.57, 1.22)	Edu	**0.60 (0.47, 0.76)**	1.09 (0.75, 1.55)
0.42 (0.09, 1.94)	--	--	**0.46 (0.28, 0.77)**	--	--	0.76 (0.46, 1.27)	**0.62 (0.43, 0.89)**	**0.54 (0.38, 0.76)**	**0.65 (0.51, 0.83)**	SOC	**1.82 (1.39, 2.39)**

1.24 (0.26, 5.81)	--	--	1.38 (0.77, 2.40)	--	--	**2.27 (1.25, 4.04)**	**1.83 (1.16, 2.92)**	**1.61 (1.03, 2.45)**	**1.92 (1.33, 2.75)**	**2.96 (2.22, 3.94)**	Tec
B											
Att + Tec	--	--	--	--	--	--	--	--	--	--	
1.29 (0.43, 3.74)	Att	--	--	--	0.74 (0.27, 1.96)	0.59 (0.22, 1.48)	0.89 (0.32, 2.31)	**0.40 (0.13, 0.98)**	**0.37 (0.17, 0.84)**	0.63 (0.22, 1.90)	
24.10 (4.45, 135.58)	**18.71 (4.48, 86.42)**	Rew + Tec	--	--	--	--	--	--	--	--	
1.07 (0.24, 4.54)	0.84 (0.26, 2.57)	**0.04 (0.01, 0.26)**	Rew	--	--	--	--	--	--	--	
1.62 (0.29, 8.94)	1.27 (0.30, 5.32)	**0.07 (0.01, 0.47)**	1.51 (0.26, 8.54)	Edu + Att + Rew	--	--	--	--	--	--	
1.60 (0.49, 5.09)	1.24 (0.61, 2.49)	**0.07 (0.01, 0.29)**	1.48 (0.44, 5.17)	0.97 (0.21, 4.39)	Edu + Att + Tec	0.80 (0.33, 1.80)	1.22 (0.49, 2.89)	0.55 (0.19, 1.33)	0.54 (0.24, 1.07)	0.86 (0.31, 2.54)	
1.12 (0.36, 3.42)	0.87 (0.49, 1.58)	**0.05 (0.01, 0.20)**	1.04 (0.33, 3.39)	0.69 (0.16, 3.05)	0.71 (0.33, 1.49)	Edu + Att	1.50 (0.71, 3.32)	0.70 (0.29, 1.43)	0.69 (0.38, 1.16)	1.09 (0.46, 2.95)	
1.39 (0.48, 3.93)	1.08 (0.69, 1.67)	**0.06 (0.01, 0.23)**	1.28 (0.44, 3.90)	0.85 (0.21, 3.56)	0.87 (0.46, 1.67)	1.23 (0.73, 2.10)	Edu + Tec	0.46 (0.17, 1.03)	**0.45 (0.23, 0.80)**	0.72 (0.28, 1.98)	
1.34 (0.46, 3.75)	1.04 (0.70, 1.54)	**0.06 (0.01, 0.22)**	1.24 (0.42, 3.73)	0.81 (0.20, 3.40)	0.84 (0.44, 1.60)	1.19 (0.72, 1.96)	0.97 (0.68, 1.35)	Edu	0.97 (0.54, 2.01)	1.56 (0.66, 4.90)	
0.78 (0.28, 2.14)	**0.61 (0.42, 0.89)**	**0.03 (0.01, 0.13)**	0.73 (0.26, 2.13)	0.48 (0.12, 1.96)	**0.49 (0.27, 0.88)**	0.70 (0.44, 1.11)	**0.56 (0.44, 0.72)**	**0.59 (0.45, 0.76)**	SOC	1.61 (0.82, 3.64)	
1.30 (0.47, 3.58)	1.02 (0.65, 1.61)	**0.05 (0.01, 0.21)**	1.22 (0.41, 3.69)	0.80 (0.19, 3.33)	0.82 (0.44, 1.56)	1.17 (0.68, 1.98)	0.94 (0.67, 1.32)	0.98 (0.69, 1.41)	**1.67 (1.31, 2.16)**	Tec	

Effect sizes are reported as OR (with 95% CrI). Comparisons are read from left to right (row to column above, column to row below) (e.g. the effect of Edu to SOC is 0.60 in 0-3 months). An OR <1 indicates a more effective intervention. Bold data comparisons are statistically significant. Edu: educational, Att: attitudinal, Tec: technical, Rew: rewards, SOC: standard of care.

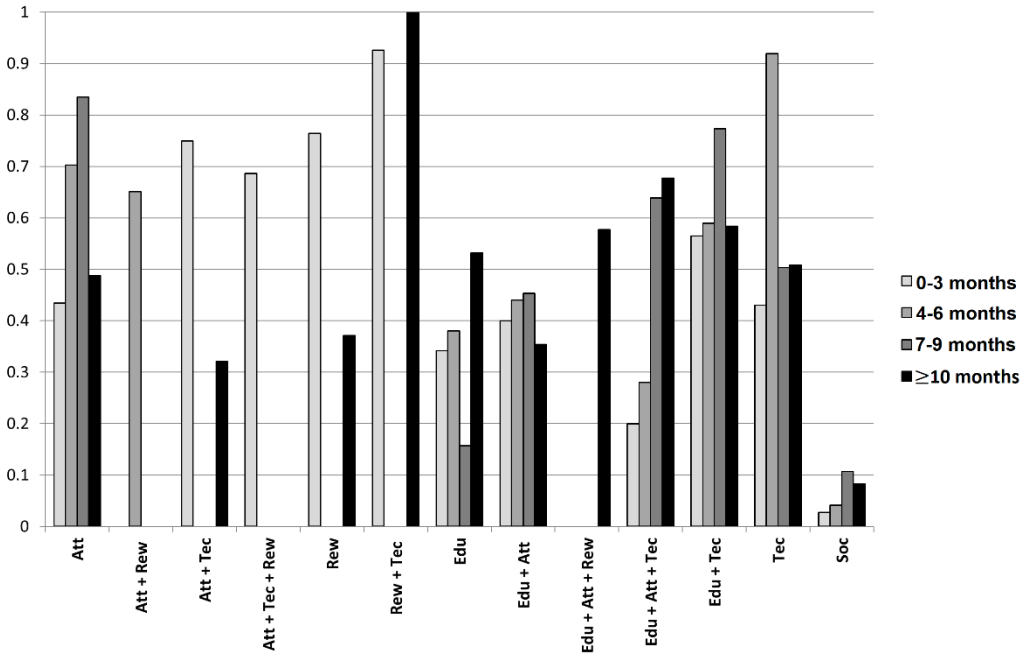

Fig 3. Summary of the effectiveness of the interventions over time considering the SUCRA analysis. SUCRA values can range from 0% (i.e. the intervention always ranks last) to 100% (i.e. the intervention always ranks first).

0-3 month follow-ups

The 0-3 month network included data from 99 studies (n=35,714 patients) and comprised 11 different nodes. Follow-up time varied from 0-3 months, with the most common period being 10-12 weeks (n= 25 studies), followed by 4-6 weeks (n=22 studies).

4-6 month follow-ups

The 4-6 month network included data from 104 studies (n=31,736 patients), compromising eight arms. Follow-up time varied from 4-6 months, with the majority studies using 24-26 weeks (n=54).

7-9 month follow-ups

Data from 18 studies (n=7,586 patients) were included in the 7-9 month network with standard of care and six interventions (attitudinal, educational, educational + attitudinal, educational + attitudinal + technical, educational + technical, technical). No studies reporting data on reward components were reported in the literature for this time period. Follow-up time varied from 7-9 months.

≥10 month follow-ups

Ninety-four studies were included in the ≥10 month network (n=152,372 patients) comprising 11 arms. Follow-up time varied from 10-40 months, with 12 months (n=60 studies) as the most common.

Components of interventions

Across all time periods, multiple interventions were effective and standard of care ranked last in all SUCRA analyses (mean SUCRA value 6%). Single component interventions were found to be the most effective in follow-ups of 4-6 months and 7-9 months, with technical (SUCRA value 92%) (OR 0.33, [95% CrI 0.25-0.45] vs SOC) and attitudinal (SUCRA value 84%) (OR 0.37, [95% CrI 0.17-0.84] vs. SOC) ranking first in each time period respectively. The combination of educational + technical components consistently performed well, with an average SUCRA value around 63%, and was always more effective than educational components alone (highest SUCRA value 53% in ≥10 month follow-ups). The addition of an attitudinal component to educational + technical components past 10 months increased effectiveness (attitudinal + educational + technical OR 0.49, [95% CrI 0.27-0.88] vs SOC; educational + technical OR 0.56 [95% CrI 0.44-0.72] vs SOC). Rewards + technical was considered an effective intervention in the shortest time period (0-3 months; n=1 study) and longest (≥10 months; n=1) (92% and 100% in the SUCRA analysis respectively) and presented significant statistical differences compared to almost all interventions and standard of care (OR 0.03, [95% CrI 0.01-0.13]

vs. SOC). However, conclusions cannot be determined on this combination based on the limited amount of evidence. Other combinations including reward components were also limited, appearing in only seven studies across all time periods with no statistically significant comparisons.

Changes over time

To facilitate data interpretation, Fig 3 shows a summary of the changes in the position of rank order for each intervention over time (for final rank orders see S6 Table). Considering only the interventions reporting data on all four time periods, educational + attitudinal + technical presented increasing comparative effectiveness over time, with a final SUCRA value reaching around 68% (median 46%, interquartile range [IQR] 26.0%-64.8%). Attitudinal interventions also presented increasing values through time up until the 7-9 month follow-ups, though dropped in effectiveness ≥10 months without the addition of other components. Technical interventions presented consistent values during the time periods (around 50% probability), except for the 4-6 month time period. In follow-ups less than 10 months, educational had a mean 29% chance of being the best option, but this value increased to 53% past 10 months (median 36%, IQR 30.0%-42.0%). The effectiveness of the interventions educational + attitudinal and educational + technical were relatively stable during all time periods at around 40% (IQR 39.0%-44.3%) and 63% (IQR 58.0%-64.0%), respectively. For attitudinal + rewards, attitudinal + technical, attitudinal + technical + rewards, rewards and educational + attitudinal + rewards further extrapolation was not possible due to the lack of studies reporting data for all follow-up periods.

Sensitivity analyses

Overall, studies' sample sizes were found to have low influence on the comparative effectiveness of interventions. Analyses that included only studies with more than 30 patients presented equivalent results compared to the original analyses for all four time periods. Results from sensitivity analyses of articles published before 2007 or after 2007 showed that for follow-ups ≥10 months, differences in the position of the interventions in the rank order were observed compared to the original analyses. These, however,

were similar to those obtained in the original analyses for shorter time periods. When evaluating studies published before 2007, the comparisons attitudinal vs. standard of care and educational + attitudinal + technical vs. standard of care lose their statistical significance with the enlargement of the 95% CrI (OR 0.81 [95% CrI 0.38-1.74] and OR 0.89 [95% CrI 0.19-4.13], respectively). By removing these studies from the original analyses and accounting for studies published after 2007, both interventions became statistically superior to standard of care (0.56 [0.35-0.89] and 0.44 [0.22-0.83], respectively) with final SUCRA values of 67% and 83%, respectively. No other significant differences were observed (S1 File).

Discussion

By using NMAs to synthesise evidence from more than 200 studies on medication adherence, we found that time significantly influenced some interventions, while having no influence on others. We found a trend towards any intervention, either singly or in combination, being more effective than standard of care, although in many cases the trend did not reach statistical significance. This review demonstrated that multicomponent interventions including educational, attitudinal and technical aspects are more effective than single component interventions. This supports other research in adherence [11], pharmacology [35] and health care more broadly [36], and is logically reinforced by the idea that adherence is a multifaceted and complex issue [6, 14]. While other adherence research has shown this by indirect comparison to standard of care [20], our research has shown this by direct comparison, albeit through an estimate.

The comparative effectiveness of complex, multicomponent interventions is not surprising. But it raises the question of how to focus our efforts on the best combination of interventions. We found that an adherence intervention that included a technical component, either singly or in combination, showed benefits that were consistent across time, which builds on other research about effectiveness [19, 21]. A technical component, such as reminders and feedback from healthcare professionals, can be an effective and inexpensive opportunity to add to standard practice to improve adherence

[37]. Reward components were found effective when present in the networks, especially when combined with technical components. However, due to the lack of studies and evidence of interventions including reward components, it is not reasonable to draw conclusions or recommendations.

This review also revealed the effectiveness of interventions with an attitudinal or educational component increased with time, but declined after 10 months when used alone. However, they continued to become more effective past 10 months when in combination with other components. A possible explanation is that while attitudinal change is important, its effect is difficult to sustain without other elements. Similar themes have been found in other areas of public health and psychology [36, 38]. Brehm's motivational intensity theory states importance and difficulty of a goal determines motivation [39]. Educational intervention components may be necessary for patients to understand the importance of adherence while technical components can simplify the medication taking process. Thus, this allows motivation from attitudinal components to fully develop and be sustained.

Many studies have shown that adherence declines over time [16, 17, 21]. This research shows for the first time that the approach needed to support adherence may change over time. Adherence to medication should not be considered a fixed concept, as it is multi-dimensional in nature. The complexity of medication adherence behaviors are reflected in the adherence taxonomy proposed by the ABC (Ascertaining Barriers for Compliance) Project Team [14] and the five dimensions of medication adherence classified by WHO [40-42]. We have demonstrated in this review that interventions to improve adherence can have an impact that varies depending on the time at which they are used. With more than half of American adults having at least one chronic condition [43], and with many of these conditions requiring long-term management [44, 45], future efforts must be focused on interventions inducing adherence change that is sustained for long periods.

Our strengths of this study are found in our statistical approach used. Network meta-analysis creates more powerful and robust evidence compared to standard meta-

analysis by using both direct and indirect evidence [23]. All the built networks demonstrated robustness with no significant inconsistency between direct and indirect comparisons found. This is also the first network of its kind to evaluate adherence across all clinical conditions in addition to looking at variations in effectiveness of interventions across time. By acknowledging that adherence is a multi-dimensional topic affected by multiple factors including therapy-related, condition-related, health system-related, socio-economic-related, and patient-related factors [7], we aimed to create a broader picture of the landscape of medication adherence. This was achieved by evaluating the patterns and changes of the effect of intervention components comprehensively across all clinical conditions over time, by not limiting our research to a clinical condition, a setting or a specific intervention type. Previous research demonstrated that the effectiveness of interventions may be related to the clinical condition [13]. Although including different clinical conditions in the network meta-analysis may be considered as a drawback due the potential heterogeneity induced, in our research, the four periods of evaluation contain an almost identical mix of medical conditions. Additionally, the heterogeneity between trials was below 70% in the vast majority of the comparisons, which is not unexpected when gathering evidence about complex interventions. Moreover, we evaluated intervention effects on all clinical conditions over time to account for the fact that determinants and issues of non-adherence are often comparable across medications and disease states. [11, 12]. While our networks were large and with many direct comparisons and a concern for heterogeneity, we can be confident in our networks due to no evidence of inconsistency being found in node-splitting analysis of direct and indirect evidence. Future research efforts should continue to expand on this landscape, including the effects of time on adherence as well as aiming to achieve the goal of long-term sustainability of improved adherence. Furthermore, sustainability of improved adherence first requires implementation of adherence enhancing interventions [46], a difficult process into the already overextended and resource-deficient practice of routine health care [45]. While multiple intervention components may be necessary for maintenance of adherence, too many components

may overwhelm and produce a negative effect [47]. To support the thinking of policy-makers and healthcare professionals, we must determine where the best compromise in complex interventions lie for cost-effective and resource-limited approaches.

Our review has limitations. One is a lack of data across all combinations, with few trials available for some interventions and not all possible combinations of components being evaluated. Moreover, not all interventions or combinations were presented across all time periods, preventing a full narrative of temporal trends. The methodological quality of the included trials was mostly unclear, with a lack of complete outcome data or poor description of the study methodology definition of the evaluated interventions, and how they were delivered. Thus, only 53.2% of the studies could be part of the quantitative synthesis as they properly reported categorical results on patient's adherence.

Additionally, only studies measuring implementation adherence were included, as initial review of the literature did not reveal enough studies reporting initiation and persistence adherence. To assist interpretability, the adherence-enhancing interventions were grouped into categories based on previous literature, but we acknowledge that a different approach of categorization may alter some results. Finally, while we decided to categorize a trial arm as standard of care if it was so determined as such by the individual study, we understand the definition of standard of care may vary by country or healthcare system.

Conclusions

In conclusion, the results from this systematic review and network meta-analysis demonstrate several interventions including educational, attitudinal, technical and multicomponent strategies are effective in enhancing medication adherence. Multicomponent interventions incorporating educational, attitudinal, and technical aspects demonstrated greater sustainability of adherence over time. Technical interventions remained consistent in effectiveness across follow-up periods, while educational and attitudinal interventions were more effective with longer follow-up times, suggesting they may take more time to reach their potential in improving

medication adherence. This research can be used to guide policy-makers and healthcare professionals in selecting effective multicomponent interventions, while future research should evaluate cost-effectiveness of these interventions.

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Supporting Information

S1 Table. Complete search strategy

S2 Table. Category definitions

S1 Appendix. Complete references

a. **Included meta-analyses**
b. **Included primary studies**
c. **Excluded primary studies**
d. **Studies included in the network meta-analysis**

S1 Fig. Risk of bias graph

S3 Table. Risk of bias summary

S4 Table. Heterogeneity between trials comparisons for the composite measure

S5 Table. Node-splitting analyses

S2 Fig. SUCRA analyses

S1 File. Sensitivity and sub-group analyses

S6 Table. Final rank orders from SUCRA analyses

S2 File. PRISMA Checklist

S3 File. PRISMA NMA Checklist

S1 Table. Complete search strategy and category definitions

Search strategy

PubMed	**#1** ("drug therapy"[Mesh Terms] OR "medication[Title/Abstract]) AND ("patient compliance"[Mesh Terms] OR "medication adherence"[Mesh Terms] OR "medication adherence"[Title/Abstract]) **#2** "systematic review"[Title/Abstract] OR "meta-analysis"[Publication type] OR "meta-analysis"[Title/Abstract] **#1 AND #2**

S2 Table. Category definitions

Category	Definition
Educational	Every intervention where a professional provided any kind of knowledge (e.g. medication information, disease state information, importance of adherence information), in any form (e.g. written, oral, in group, by telephone), to a patient with the aim of modifying patient's beliefs, attitudes or skills that facilitate adherence.
Attitudinal	Interventions aiming to modify behavioral intention (theory of planned behavior) based on modifying patient's attitudes or subjective norm, delivered in any form (e.g. written, oral, in group, by telephone).
Technical	Interventions providing any gadget, instrument, or system that facilitate the medication intake, through reminders, regime simplifications, follow-ups, direction observation therapy, self-monitoring, cue-dose training, feedback etc.
Rewards	Interventions that produce awards (or penalties) associated to a better (or worst) medication adherence.

S1 Appendix. Complete references

e. Included meta-analyses

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g. Excluded primary studies

Original studies	**Excluded**
Quilici, 2013	Non-experimental study
Gould, 2011	Non-experimental study
Simoni, 2011	Undefined/excluded outcomes
Berger, 2003	Undefined/excluded outcomes
Awofeso, 1995	Non-experimental study
Becker, 1986	Undefined/excluded outcomes
Kennedy, 1990	Non-experimental study
Levensky, 2006	Non-experimental study
MacDonald, 1977	Undefined/excluded outcomes
Qingjun, 1998a	Included pediatrics
Revankar, 1993	Included pediatrics
Spriet, 1980	Non-experimental study
Traiger, 1997	Undefined/excluded outcomes
Hosie, 1995	Undefined/excluded outcomes
Lennon, 2008	Included pediatrics
Adam, 2001	Included pediatrics
Garcia Callejo, 1998	Included pediatrics
Clegg, 2006	Included pediatrics
Ballantyne, 1985	Out of scope
Linder, 1993	Included pediatrics
Gooch, 1997	Included pediatrics
Edelstein, 1993	Included pediatrics
Owen, 1993	Included pediatrics
Venuta, 1998	Included pediatrics
Disney, 1990	Included pediatrics
Mita, 2003	Included pediatrics
Cohen, 1996	Included pediatrics
Behre, 1997	Included pediatrics
Pichichero, 1999	Included pediatrics
Gooch, 1993	Included pediatrics

Original studies	Excluded
Richard, 1981	Included pediatrics
Damrikarnlert, 2000	Included pediatrics
Gerber, 1985	Included pediatrics
Gehanno, 1994	Included pediatrics
Cook, 1996	Included pediatrics
Dawson, 1998	Non-experimental study
Nimpitakpong, 2002	Non-experimental study
Nucifora, 2006	Undefined/excluded outcomes
Powell, 2010	Undefined/excluded outcomes
Tierney, 2003	Non patient-targeted interventions
Clarkin, 1998	Out of scope
Colom, 2003	Undefined/excluded outcomes
Lenz, 2010	Non-experimental study
Maneesakorn, 2007	Undefined/excluded outcomes
von Bormann, 2015	Undefined/excluded outcomes
Austin, 1986	Non-experimental study
Cook, 2010	Undefined/excluded outcomes
De Geest, 2006	Undefined/excluded outcomes
Freedman, 2007	Non-experimental study
Harper, 1984	Undefined/excluded outcomes
Matterson, 2011	Non-experimental study
Mitchell, 1992	Non-experimental study
Moitra, 2011	Undefined/excluded outcomes
Nietert, 2009	Non patient-targeted interventions
Oser, 2008	Non-experimental study
Stewart, 2008	Non-experimental study
Watakakasol, 2010	Non-experimental study
Wu, 2006	Undefined/excluded outcomes
Zuckerman, 2004	Non patient-targeted interventions
Christensen, 2010	Undefined/excluded outcomes
Chung, 2011	Undefined/excluded outcomes
Franklin, 2006	Included pediatrics
Rothschild, 2014	Undefined/excluded outcomes
Zolfaghari, 2012	Non-experimental study
Walker, 2011	Undefined/excluded outcomes
Benson, 2004	Out of scope
Parienti, 2007	Undefined/excluded outcomes
Rode, 2008	Non-experimental study
Ruane, 2006	Undefined/excluded outcomes
Tulsky, 2000	Undefined/excluded outcomes
Bock, 2001	Undefined/excluded outcomes
Morisky, 2001	Undefined/excluded outcomes
Jakubowiak, 2007	Undefined/excluded outcomes
Martins, 2009	Undefined/excluded outcomes
Grabowski, 1979	Undefined/excluded outcomes
Preston, 1999	Undefined/excluded outcomes
Carroll, 2001	Out of scope
Carroll, 2002	Out of scope

Original studies	Excluded
Seal, 2003	Excluded medication
Stitzer, 2010	Excluded medication
Claassen, 2007	Undefined/excluded outcomes
Berger, 2005	Undefined/excluded outcomes
George, 2010	Non-experimental study
Hovell, 2003	Included pediatrics
Sheeran, 1999	Included pediatrics
Van Es, 2001	Included pediatrics
Engelbrecht, 2010	Non-experimental study
Sabin, 2014	Non-experimental study
Davies, 2010	Non-experimental study
Wilson, 2010	Non patient-targeted interventions
Adler, 2004	Undefined/excluded outcomes
Lai, 2010	Non-experimental study
Heilmann, 2012	Out of scope
Ting, 2012	Included pediatrics
Cook, 2010	Non-experimental study
Stockl, 2010	Out of scope
Stockl, 2010b	Out of scope
Tamone, 2012	Non-experimental study
Downey, 2006	Non-experimental study
Marteau, 2012	Out of scope
Smith, 2013	Excluded medication
Musser, 2001	Non-experimental study
RCTAI, 1989	Non-experimental study
Hulsbosch, 2008	Non-experimental study
Jones, 2007	Undefined/excluded outcomes
Tuldra, 2002	Undefined/excluded outcomes
Maasland, 2007	Undefined/excluded outcomes
Armstrong, 2009	Excluded medication
Cococila, 2009	Undefined/excluded outcomes
Yentzer, 2011	Non-experimental study
Binstock, 1988	Undefined/excluded outcomes
Huang, 2000	Excluded medication
Jansen, 2009	Undefined/excluded outcomes
Kripalani, 2007	Undefined/excluded outcomes
Simmons, 2000	Undefined/excluded outcomes
Suppapitiporn, 2005	Undefined/excluded outcomes
Dezii, 2000	Non-experimental study
NDC data set	Non-experimental study
Melikian, 2002	Non-experimental study
Knobel, 1999	Undefined/excluded outcomes
Kelly, 1988	Undefined/excluded outcomes
Nicoleau, 1985	Non-experimental study
Zhao, 2004	Non-experimental study
Lourenco, 2011	Non-experimental study
Campbell, 1998	Undefined/excluded outcomes
Gould, 2011	Non-experimental study

Original studies	Excluded
Lehr, 1986	Non-experimental study
Muniz, 2010	Undefined/excluded outcomes
Shemesh, 2006	Undefined/excluded outcomes
Yilmaz, 2005	Undefined/excluded outcomes
Anderson, 2004	Out of scope
Austin, 1986	Non-experimental study
Bogart, 2012	Undefined/excluded outcomes
Freedman, 2007	Non-experimental study
Harper, 1984	Undefined/excluded outcomes
Laine, 1996	Undefined/excluded outcomes
Mann, 2001	Out of scope
Martin, 2011	Undefined/excluded outcomes
Moitra, 2011	Undefined/excluded outcomes
Mundy, 2009	Non-experimental study
Newsome, 1995	Non-experimental study
Powell, 2002	Non-experimental study
Tagliacozzo, 1974	Undefined/excluded outcomes
Vivian, 2002	Undefined/excluded outcomes
Webel, 2010	Undefined/excluded outcomes
Werner, 1979	Non-experimental study
Fujii, 1985	Non-experimental study
Eisen, 1990	Non-experimental study
Halpern, 1993	Excluded medication
Brun, 1994	Non-experimental study
Halfmann, 2000	Non-experimental study
Jennings, 1992	Non-experimental study
Rimer, 1987	Undefined/excluded outcomes
Wood, 1989	Undefined/excluded outcomes
Eisen, 1990	Non-experimental study
Girvin, 1999	Non-experimental study
Berkovitch, 1998	Included pediatrics
Rapoff, 2002	Included pediatrics
Grosset, 2007	Non-experimental study
Ducharme, 2011	Included pediatrics
Bonner, 2002	Included pediatrics
Canino, 2008	Included pediatrics
Morisky, 2001	Undefined/excluded outcomes
Schwartz-Lookinland, 1989	Included pediatrics
Yin, 2008	Included pediatrics
Armour, 2004	Undefined/excluded outcomes
Berrien, 2004	Included pediatrics
Bertakis, 1986	Included pediatrics
Colcher, 1972	Included pediatrics
Ellison, 1982	Included pediatrics
Eriksson, 1998	Out of scope
Finney, 1985	Included pediatrics
Gibbs, 1989	Undefined/excluded outcomes
Jameson, 1995	Undefined/excluded outcomes

Original studies	Excluded
Levesque, 1983	Out of scope
Linszen, 1996	Included pediatrics
McCrindle, 1997	Included pediatrics
Mengze, 1994	Undefined/excluded outcomes
Sanmarti, 1993	Included pediatrics
Sellors, 1997	Undefined/excluded outcomes
Sharpe, 1974	Undefined/excluded outcomes
Smith, 1986	Included pediatrics
Spriet, 1980	Non-experimental study
Tinkelman, 1980	Included pediatrics
Williams, 1986	Included pediatrics
Al Owaish, 1985	Non-experimental study
Avanzini, 2002	Non patient-targeted interventions
Beeson, 1977	Non-experimental study
Cooper, 2011	Non patient-targeted interventions
Evans, 1986	Non patient-targeted interventions
Fletcher, 1975	Undefined/excluded outcomes
Gomez-Marcos, 2006	Non patient-targeted interventions
Harowski, 1983	Non-experimental study
Harper, 1984	Undefined/excluded outcomes
Hess, 2007	Undefined/excluded outcomes
Inui, 1976	Non patient-targeted interventions
Jafar, 2009	Undefined/excluded outcomes
Kobalava, 2010	Non-experimental study
Leung, 2012	Non-experimental study
Magadza, 2009	Non-experimental study
Martin, 2011	Undefined/excluded outcomes
Muhlhauser, 1988	Undefined/excluded outcomes
Murray, 2004	Undefined/excluded outcomes
Oparah, 2006	Non-experimental study
Patel, 2013	Non-experimental study
Pertusa Martinez, 1998	Non-experimental study
Pierce, 1984	Undefined/excluded outcomes
Pippalla, 1994	Non-experimental study
Resnick, 2009	Non-experimental study
Roca-Cusachs, 1991	Undefined/excluded outcomes
Rodriguez, 2011	Non-experimental study
Roumie, 2006	Non patient-targeted interventions
Santschi, 2008	Non-experimental study
Sicras-Mainar, 2013	Non-experimental study
Stewart, 2005	Undefined/excluded outcomes
Stewart, 2008	Undefined/excluded outcomes
van de Steeg-van Gompel, 2010	Non patient-targeted interventions
Wentzlaff, 2011	Undefined/excluded outcomes
Patel, 2015	Undefined/excluded outcomes
van Bruggen, 2009	Non-experimental study
Aslani, 2011	Undefined/excluded outcomes
Flemming, 2013	Undefined/excluded outcomes

Original studies	Excluded
Bangsberg, 2009	Non-experimental study
Hornung, 1996	Undefined/excluded outcomes
Pitschel-Walz, 2006	Excluded medication
Williams-a, 2012	Undefined/excluded outcomes
Kender, 2010	Non-experimental study
Martino, 2006	Undefined/excluded outcomes
Macalino, 2007	Undefined/excluded outcomes
Crowley, 2013	Undefined/excluded outcomes
Greer, 2011	Non-experimental study
Margolius, 2012	Undefined/excluded outcomes
Duncan, 2013	Included pediatrics
Otsuki, 2009	Included pediatrics
Hederos, 2005	Included pediatrics
Bender, 2014	Included pediatrics
Liu, 2007	Undefined/excluded outcomes
Ostojic, 2005	Undefined/excluded outcomes
Ryan, 2012	Undefined/excluded outcomes
Chisholm-Burns, 2013	Undefined/excluded outcomes
Fennell, 1994	Included pediatrics
Babigumira, 2011	Non-experimental study
Jaffar, 2009	Undefined/excluded outcomes
Sherrard, 2015	Undefined/excluded outcomes
Belzer, 2014	Included pediatrics
Duncan, 2012	Out of scope
Garcia, 2005	Undefined/excluded outcomes
Naar-King, 2013	Included pediatrics
Orrell, 2015	Included pediatrics
Wamalwa, 2009	Included pediatrics
Yu, 2012	Non-experimental study
Heisig, 2015	Non-experimental study
Graetz, 2017	Non-experimental study
Ell, 2009	Undefined/excluded outcomes
Giallauria, 2009	Undefined/excluded outcomes
Giannuzzi, 2008	Undefined/excluded outcomes
Jorstad, 2013	Undefined/excluded outcomes
Lapointe, 2006	Undefined/excluded outcomes
Miller, 1988	Undefined/excluded outcomes
Redfern, 2008	Undefined/excluded outcomes
Yorio, 2008	Undefined/excluded outcomes
Charrois, 2006	Undefined/excluded outcomes
Cordina, 2001	Included pediatrics
Xaubet Olivera, 2016	Undefined/excluded outcomes
Aluisio, 2011	Out of scope
Kalembo, 2013	Undefined/excluded outcomes
Turan, 2015	Undefined/excluded outcomes

Original studies	Excluded
Stinson, 2013	Undefined/excluded outcomes
Kim, 2015	Undefined/excluded outcomes
Dillabaugh, 2012	Undefined/excluded outcomes
Kirsten, 2011	Undefined/excluded outcomes
Mepham, 2011	Non-experimental study
ENHAT-CS, 2014	Non-experimental study
Weiss, 2013	Undefined/excluded outcomes
Okonji, 2012	Non-experimental study
Herlihy, 2015	Undefined/excluded outcomes
Richter, 2014	Undefined/excluded outcomes
Le Roux, 2013	Undefined/excluded outcomes
Kieffer, 2011	Undefined/excluded outcomes
Matthews, 2016	Out of scope
Yotebieng, 2016	Out of scope
Finocchario-Kessler, 2014	Undefined/excluded outcomes
Nyamathi, 2012	Undefined/excluded outcomes

h. Studies included in the network meta-analysis

0-3 months

Study ID	Title	Study size	Interventions
Berg, 2011	Use of peers to improve adherence to antiretroviral therapy: a global network meta-analysis	77	Technical 1st, Standard care 1st
Bessa, 2016	Efficacy of interventions for adherence to the immunosuppressive therapy in kidney transplant recipients: a meta-analysis and systematic review	124	Educational 1st, Standard care 1st
Bogner, 2008	Integration of Depression and Hypertension Treatment: A Pilot, Randomized Controlled Trial	64	Educational + Attitudinal 1st, Standard care 1st
Boissel, 1996	Comparison between a bid and a tid regimen: improved compliance with no improved antihypertensive effect	7274	Technical 1st, Standard care 1st
Capoccia, 2004	Randomized trial of pharmacist interventions to improve depression care and outcomes in primary care	74	Educational + Technical 1st, Standard care 1st
Chatkin, 2006	Impact of a Low-Cost and Simple Intervention in Enhancing Treatment Adherence in a Brazilian Asthma Sample	271	Educational 1st, Standard care 1st
Cheung, 1988	The paradox of using a 7 day antibacterial course to treat urinary tract infections in the community	77	Technical 1st, Standard care 1st
Claborn, 2014	Pilot study examining the efficacy of an electronic intervention to promote HIV medication adherence	97	Educational + Attitudinal + Technical 1st, Standard care 1st
Cochran, 1984	Preventing Medical Noncompliance in the Outpatient Treatment of Bipolar Affective Disorders	28	Attitudinal 1st , Standard care 1st
Cole, 1971	Drug consultation: its significance to the discharged hospital patient and its relevance as a role for the pharmacist	50	Educational 1st, Standard care 1st
Collier, 2005	A Randomized Study of Serial Telephone Call Support to Increase Adherence and Thereby Improve Virologic Outcome in Persons Initiating Antiretroviral Therapy	171	Educational + Attitudinal 1st, Standard care 1st
Cossette, 2012	Randomized Controlled Trial of Tailored Nursing Interventions to Improve Cardiac Rehabilitation Enrollment	243	Educational + Attitudinal 1st, Standard care 1st
Crockett, 2006	Patient outcomes following an intervention involving community pharmacists in the management of depression	106	Educational 1st, Standard care 1st
Crome, 1982	Assessment of a new calendar pack-the C-PAK	78	Technical 1st, Standard care 1st
Da Costa, 2012	Results of a randomized controlled trial to assess the effects of a mobile SMS-based intervention on treatment adherence in HIV/AIDS-infected	21	Technical 1st, Standard care 1st

	Brazilian women and impressions and satisfaction with respect to incoming messages		
Detry, 1995	Patient compliance and therapeutic coverage: comparison of amlodipine and slow release nifedipine in the treatment of hypertension	640	Technical 1st, Standard care 1st
Dilorio, 2009	A telephone-based self-management program for people with epilepsy	22	Educational + Attitudinal 1st, Educational 1st
Eker, 2012	Effectiveness of six-week psychoeducation program on adherence of patients with bipolar affective disorder	71	Educational + Attitudinal 1st, Standard care 1st
Elixhauser, 1990	The Effects of 'Monitoring and Feedback on Compliance	90	Technical 1st, Standard care 1st
Elkjaer, 2010	E-health empowers patients with ulcerative colitis: a randomised controlled trial of the web-guided 'Constant-care' approach	333	Educational 1st, Standard care 1st
Eron, 2000	Efficacy, safety, and adherence with a twice-daily combination lamivudine/zidovudine tablet formulation, plus a protease inhibitor, in HIV infection	223	Technical 1st, Standard care 1st
Eshelman, 1976	Effect of packging on patient compliance with na antihypertensive medication	100	Technical 1st, Standard care 1st
Faulkner, 2000	Impact of Pharmacy Counseling on Compliance and Effectiveness of Combination Lipid-Lowering Therapy in Patients Undergoing Coronary Artery Revascularization: A Randomized, Controlled Trial	30	Educational 1st, Standard care 1st
Fisher, 2011	Computer-Based Intervention in HIV Clinical Care Setting Improves Antiretroviral Adherence: The LifeWindows Project	328	Attitudinal 1st , Standard care 1st
Fulmer, 1999	An Intervention Study to Enhance Medication Compliance in Community-Dwelling Elderly Individuals	42	Technical 1st, Standard care 1st
Fyllingen, 1991	Phenoxymethylpenicillin Two or Three Times Daily in Bacterial Upper Respiratory Tract Infections: A Blinded, Randomized and Controlled Clinical Study	131	Technical 1st, Standard care 1st
Gabriel, 1977	Improved Patient Compliance through Use of a Daily Drug Reminder Chart	79	Technical 1st, Standard care 1st
Garcia, 2015	Behavioral measures to reduce non-adherence in renal transplant recipients: a prospective randomized controlled trial	111	Educational 1st, Standard care 1st
García-Cardenas, 2013	Effect of a pharmacist intervention on asthma control. A cluster randomised trial	336	Educational + Attitudinal 1st, Standard care 1st
Girvin, 1999	A comparison of enalapril 20 mg once daily versus 10 mg twice daily in terms of blood pressure lowering and patient compliance Briegeen Girvin,	27	Technical 1st, Standard care 1st
Golin, 2006	A 2-Arm, Randomized, Controlled Trial of a Motivational Interviewing–Based Intervention to Improve Adherence to Antiretroviral Therapy (ART) Among Patients Failing or Initiating	117	Educational + Attitudinal 1st, Educational 1st

Gonzalez-Fernandez, 1990	Usefulness of a Systemic Hypertension In-Hospital Educational Program	47	Educational 1st, Standard care 1st
Goswami, 2013	Impact of an integrated intervention program on atorvastatin adherence: a randomized controlled trial	208	Educational 1st, Standard care 1st
Henry, 1999	Enhancing Compliance Not a Prerequisite for Effective Eradication of Helicobacter pylori: The HelP Study	117	Educational + Technical 1st, Standard care 1st
Hilleman, 1993	Conversion from Sustained-Release to Immediate-Release Calcium Entry Blockers: Outcome in Patients with Mild-to-Moderate Hypertension	82	Technical 1st, Standard care 1st
Ho, 2008	Effect of audible and visual reminders on adherence in glaucoma patients using a commercially available dosing aid	42	Technical 1st, Standard care 1st
Holzemer, 2006	Testing a Nurse-Tailored HIV Medication Adherence Intervention	180	Educational + Attitudinal 1st, Standard care 1st
Horvath, 2013	Feasibility, Acceptability and Preliminary Efficacy of an Online Peer-to-Peer Social Support ART Adherence Intervention	123	Educational + Attitudinal + Technical 1st, Standard care 1st
Ingersoll, 2011	A Pilot Randomized Clinical Trial of Two Medication Adherence and Drug Use Interventions For HIV+ Crack Cocaine Users*	42	Attitudinal 1st , Educational 1st
Johnson, 2011	Improving Coping Skills for Self-management of Treatment Side Effects Can Reduce Antiretroviral Medication Nonadherence among People Living with HIV	249	Educational + Attitudinal 1st, Standard care 1st
Khonsari, 2015	Effect of a reminder system using an automated short message service on medication adherence following acute coronary syndrome	62	Technical 1st, Standard care 1st
Kim, 2013	Effects of a web-based stroke education program on recurrence prevention behaviors among stroke patients: a pilot study	36	Educational 1st, Standard care 1st
Klang, 2015	Community pharmacists' support improves antidepressant adherence in the community	12919	Technical 1st, Standard care 1st
Koenig, 2008	Randomized Controlled Trial of an Intervention to Prevent Adherence Failure Among HIV-Infected Patients Initiating Antiretroviral Therapy	226	Educational + Attitudinal + Technical 1st, Standard care 1st
Kotowycz, 2010	Safety and feasibility of early hospital discharge in ST-segment elevation myocardial infarction	54	Educational 1st, Standard care 1st
Kronish, 2012	The Effect of Enhanced Depression Care on Adherence to Risk Reducing Behaviors after Acute Coronary Syndromes: Findings from the COPES Trial	157	Attitudinal 1st , Standard care 1st
Kubota, 2006	Short-term Safety and Tolerability of a Once-Daily Fixed-Dose Abacavir-Lamivudine Combination versus Twice-Daily Dosing of Abacavir and Lamivudine as Separate Components: Findings from the ALOHA Study	680	Technical 1st, Standard care 1st

Lee, 1999	A Randomized Controlled Trial of an Enhanced Patient Compliance Program for Helicobacter pylori Therapy	125	Educational + Technical 1st, Standard care 1st
Lopez Cabezas, 2006	Randomized clinical trial of a postdischarge pharmaceutical care program vs. regular follow-up in patients with heart failure	94	Educational 1st, Standard care 1st
Lv, 2012	A mobile phone short message service improves perceived control of asthma: a randomized controlled trial	71	Educational 1st, Educational + Technical 1st, Standard care 1st
MacIntosh, 2007	A comparison of patient adherence and preference of packaging method for oral anticancer agents using conventional pill bottles versus daily pill boxes	42	Technical 1st, Standard care 1st
Maduka, 2013	Adherence counseling and reminder text messages improve uptake of antiretroviral therapy in a tertiary hospital in Nigeria	104	Educational + Attitudinal + Technical 1st, Standard care 1st
Marquez Contreas, 2004	Effectiveness of an intervention to provide information to patients with hypertension as short text messages and reminders sent to their mobile phone (HTA-Alert)	67	Educational + Technical 1st, Standard care 1st
Marquez-Contreras, 2004	Effectiveness of an Intervention to Provide Information to Patients With Hypertension as Short Text Messages of Reminders Sent to Their Mobile Phone (HTA-Alert)	67	Educational 1st, Standard care 1st
Martinot, 2001	A Comparative Study of Clarithromycin Modified Release and Amoxicillin/ Clavulanic Acid in the Treatment of Acute Exacerbation of Chronic Bronchitis	250	Technical 1st, Standard care 1st
Matsumura, 2012	Does a Combination Pill of Antihypertensive Drugs Improve Medication Adherence in Japanese?	207	Technical 1st, Standard care 1st
Mbuagbaw, 2012	Mobile phone text messages for improving adherence to antiretroviral therapy (ART): an individual patient data meta-analysis of randomised trials	200	Technical 1st, Standard care 1st
Mooney, 2005	Interventions to increase use of nicotine gum: A randomized, controlled, single-blind trial	97	Technical 1st, Rewards + Technical 1st, Standard care 1st
Mooney, 2007	Adding MEMS feedback to behavioral smoking cessation therapy increases compliance with bupropion: A replication and extension study	55	Attitudinal + Technical 1st, Attitudinal 1st
Moss, 2010	Impact of a patient-support program on mesalamine adherence in patients with ulcerative colitis — A prospective study	62	Educational + Attitudinal 1st, Standard care 1st
Najafi, 2016	The Nurse-Led Telephone Follow-Up on Medication and Dietary Adherence among Patients after Myocardial Infarction: A Randomized Controlled Clinical Trial	100	Educational 1st, Standard care 1st

Nance, 2017	Short-term effectiveness of a community health worker intervention for HIV-infected pregnant women in Tanzania to improve treatment adherence and retention in care: A cluster-randomized trial	1830	Educational 1st, Standard care 1st
Nazareth, 2001	A pharmacy discharge plan for hospitalized elderly patients – a randomized controlled trial	362	Educational + Attitudinal 1st, Standard care 1st
Nielson, 2010	Patient education in groups increases knowledge of osteoporosis and adherence to treatment: A two-year randomized controlled trial	300	Educational 1st, Standard care 1st
Ollivier, 2009	Use of short message service (SMS) to improve malaria chemoprophylaxis compliance after returning from a malaria endemic area	335	Technical 1st, Standard care 1st
Park, 1992	Medication Adherence Behaviors in Older Adults: Effects of External Cognitive Supports	61	Technical 1st, Standard care 1st
Parsons, 2007	Motivational Interviewing and Cognitive-Behavioral Intervention to Improve HIV Medication Adherence Among Hazardous Drinkers: A Randomized Controlled Trial	115	Attitudinal 1st , Educational 1st
Pearson, 2007	Randomized Control Trial of Peer-Delivered, Modified Directly Observed Therapy for HAART in Mozambique	350	Educational + Technical 1st, Standard care 1st
Polack, 2008	Evaluation of different methods of providing medication-related education to patients following	14	Educational 1st, Standard care 1st
Pullar, 1988	Use of a pharmacologic indicator to compare compliance with tablets prescribed to be taken once, twice, or three times daily	179	Technical 1st, Standard care 1st
Purcell, 2007	Results From a Randomized Controlled Trial of a Peer-Mentoring Intervention to Reduce HIV Transmission and Increase Access to Care and Adherence	430	Attitudinal 1st , Educational 1st
Ramirez-Garcia & Cote, 2012	An Individualized Intervention to Foster Optimal Antiretroviral Treatment-Taking Behavior Among Persons Living With HIV: A Pilot Randomized Controlled Trial	44	Educational + Attitudinal 1st, Standard care 1st
Raynor, 1993	Effects of computer generated reminder charts on patients' compliance with drug regimens	191	Educational 1st, Educational + Technical 1st
Rich, 1995	A multidisciplinary intervention to prevent the readmission of elderly Patients with congestive heart failure	282	Educational 1st, Standard care 1st
Rich, 1996	Effect of a Multidisciplinary Intervention on Medication Compliance in Elderly Patients with Congestive Heart Failure	156	Educational 1st, Standard care 1st
Rigsby, 2000	Cue-dose Training with Monetary Reinforcement Pilot Study of an Antiretroviral Adherence Intervention	55	Technical 1st, Attitudinal + Technical + Rewards 1st, Standard care 1st

Rinfret, 2013	Telephone contact to improve adherence to dual antiplatelet therapy after drug-eluting stent implantation	300	Educational 1st, Standard care 1st
Roden, 1985	Evaluation of two techniques to improve drug Compliance in the elderly	84	Technical 1st, Educational 1st, Standard care 1st
Rozenfeld, 1999	Assessing the Impact of Medication Consultations with a Medication Event Monitoring System	33	Educational 1st, Standard care 1st
Rubio-Valera, 2013	Evaluation of a pharmacist intervention on patients initiating pharmacological treatment for depression: A randomized controlled superiority trial	179	Educational 1st, Standard care 1st
Schaffer and Tian, 2004	Promoting Adherence Effects of Theory-Based Asthma Education	70	Educational 1st, Standard care 1st
Schmitz, 2005	Medication Compliance During a Smoking Cessation Clinical Trial: A Brief Intervention Using MEMS Feedback	97	Technical 1st, Standard care 1st
Silveira, 2014	Randomized Controlled Trial to Evaluate the Impact of Pharmaceutical Care on Therapeutic Success in HIV-Infected Patients in Southern Brazil	332	Educational 1st, Standard care 1st
Smith, 2003	A medication self-management program to improve adherence to HIV therapy regimens	43	Educational + Attitudinal 1st, Standard care 1st
Strandbygaard, 2010	A daily SMS reminder increases adherence to asthma treatment: A three-month follow-up study	22	Technical 1st, Standard care 1st
Sweeney, 1989	The impact of the clinical pharmacist on compliance in a geriatric population	103	Educational 1st, Standard care 1st
Tuldra, 2000	Prospective Randomized Two-Arm Controlled Study To Determine the Efficacy of a Specific Intervention To Improve Long-Term Adherence to Highly Active Antiretroviral Therapy	116	Attitudinal 1st , Standard care 1st
Volpp, 2008	A test of financial incentives to improve warfarin adherence	45	Rewards 1st, Standard care 1st
Wagner, 2006	Cognitive-behavioral intervention to enhance adherence to antiretroviral therapy: a randomized controlled trial (CCTG 578)	199	Attitudinal 1st , Standard care 1st
Wagner, 2013	Pilot Controlled Trial of the Adherence Readiness Program: An Intervention to Assess and Sustain HIV Antiretroviral Adherence Readiness	60	Educational + Attitudinal 1st, Standard care 1st
Wakefield, 2009	Outcomes of a home telehealth intervention for patients with heart failure	89	Educational 1st, Standard care 1st
Wang, 2014	A Randomized Controlled Trial to Assess Adherence to Allergic Rhinitis Treatment following a Daily Short Message Service (SMS)	50	Technical 1st, Standard care 1st
Williams, 2006	Home Visits to Improve Adherence to Highly Active Antiretroviral Therapy: A Randomized Controlled Trial	171	Educational + Attitudinal 1st, Standard care 1st
Williams, 2012	A multifactorial intervention to improve blood pressure control in co-existing diabetes and kidney disease: a feasibility randomized controlled trial	75	Educational + Attitudinal + Technical 1st, Standard care 1st

Wong, 2013	Effectiveness of a Pharmacist-Led Drug Counseling on Enhancing Antihypertensive Adherence and Blood Pressure Control: A Randomized Controlled Trial	231	Educational + Technical 1st, Standard care 1st
Wong, 2017	A pharmacy management service for adults with asthma: a cluster randomised controlled trial	157	Educational 1st, Standard care 1st
Wu, 2012	Effect of a Medication-Taking Behavior Feedback, Theory-Based Intervention on Outcomes in Patients with Heart Failure	82	Attitudinal 1st , Educational + Attitudinal + Technical 1st, Standard care 1st
Wyatt, 2004	The Efficacy of an Integrated Risk Reduction Intervention for HIV-PositiveWomen With Child Sexual Abuse Histories	147	Attitudinal 1st , Standard care 1st
Zillich, 2005	Hypertension Outcomes Through Blood Pressure Monitoring and Evaluation by Pharmacists (HOME Study)	125	Educational 1st, Standard care 1st

4-6 months

Study ID	Title	Study size	Interventions
Altice, 2007	Superiority of Directly Administered Antiretroviral Therapy over Self-Administered Therapy among HIV-Infected Drug Users: A Prospective, Randomized, Controlled Trial	141	Technical 2nd, Standard care 2nd
Ball, 2006	A Randomized Controlled Trial of Cognitive Therapy for Bipolar Disorder: Focus on Long-Term Change	52	Standard care 2nd, Attitudinal 2nd
Basso, 2013	Exploring ART Intake Scenes in a Human Rights-Based Intervention to Improve Adherence: A Randomized Controlled Trial	108	Standard care 2nd, Educational + Attitudinal 2nd
Berg, 2011	Directly observed antiretroviral therapy improves adherence and viral load in drug users attending methadone maintenance clinics: a randomized controlled trial*	77	Technical 2nd, Standard care 2nd
Bessa, 2016	Prospective Randomized Trial Investigating the Influence of Pharmaceutical Care on the Intra-Individual Variability of Tacrolimus Concentrations Early After Kidney Transplant	124	Educational 2nd, Standard care 2nd
Beune, 2014	Culturally Adapted Hypertension Education (CAHE) to Improve Blood Pressure Control and Treatment Adherence in Patients of African Origin with Uncontrolled Hypertension: Cluster-Randomized Trial	139	Educational 2nd, Standard care 2nd
Blenkinsopp, 2000	Extended adherence 0 support Ir by 0 community pharmac with hypertension: a controlled trial	232	Educational 2nd, Standard care 2nd
Bosworth, 2008	Take Control of Your Blood pressure (TCYB) study: A multifactorial tailored behavioral and educational intervention for achieving blood pressure control	636	Standard care 2nd, Educational + Attitudinal + Technical 2nd
Bouvy, 2003	Effect of a Pharmacist-Led Intervention on Diuretic Compliance in Heart Failure Patients: A Randomized Controlled Study	152	Educational 2nd, Standard care 2nd
Brook, 2005	A Pharmacy-Based Coaching Program to Improve Adherence to Antidepressant Treatment Among Primary Care Patients	135	Educational 2nd, Standard care 2nd
Brown, 1997	Moderate Dose, Three-Drug Therapy With Niacin, Lovastatin, and Colestipol	29	Technical 2nd, Standard care 2nd
Burrelle, 1987	Evaluation of an Interdisciplinary Compliance Service for Elderly Hypertensives	16	Standard care 2nd, Educational + Technical 2nd
Calvert, 2012	Patient-focused intervention to improve long-term adherence to evidence-based medications: A randomized trial	143	Educational 2nd, Educational + Technical 2nd

Capoccia, 2004	Randomized trial of pharmacist interventions to improve depression care and outcomes in primary care	74	Standard care 2nd, Educational + Technical 2nd
Chaisson, 2001	A Randomized, Controlled Trial of Interventions to Improve Adherence to Isoniazid Therapy to Prevent Tuberculosis in Injection Drug Users	300	Technical 2nd, Educational 2nd, Standard care 2nd
Charles, 2007	An audiovisual reminder function improves adherence with inhaled corticosteroid therapy in asthma	90	Technical 2nd, Standard care 2nd
Cochran, 1984	Preventing Medical Noncompliance in the Outpatient Treatment of Bipolar Affective Disorders	28	Standard care 2nd, Attitudinal 2nd
Costa, 2008	Transdiciplinary approach to the follow-up of patients after myocardial infarction	142	Educational 2nd, Standard care 2nd
Da Costa, 2012	Results of a randomized controlled trial to assess the effects of a mobile SMS-based intervention on treatment adherence in HIV/AIDS-infected Brazilian women and impressions and satisfaction with respect to incoming messages	21	Technical 2nd, Standard care 2nd
Eron, 2000	Efficacy, safety, and adherence with a twice-daily combination lamivudine/zidovudine tablet formulation, plus a protease inhibitor, in HIV infection	223	Technical 2nd, Standard care 2nd
Evans, 2010	The Collaborative Cardiovascular Risk Reduction in Primary Care (CCARP) Study	176	Standard care 2nd, Educational + Technical 2nd
Falces, 2008	[An educative intervention to improve treatment compliance and to prevent readmissions of elderly patients with heart failure]	103	Educational 2nd, Standard care 2nd
Finley, 2003	Impact of a Collaborative Care Model on Depression in a Primary Care Setting: A Randomized Controlled Trial	125	Standard care 2nd, Educational + Technical 2nd
Foster, 2014	Inhaler reminders improve adherence with controller treatment in primary care patients with asthma	129	Technical 2nd, Educational 2nd, Standard care 2nd, Educational + Technical 2nd
Gamble, 2011	A study of a multi-level intervention to improve non-adherence in difficult to control asthma	18	Standard care 2nd, Educational + Attitudinal 2nd
García-Cardenas, 2013	"Effect of a pharmacist intervention on asthma control. A cluster randomised trial"	336	Standard care 2nd, Educational + Attitudinal 2nd

Geiter, 1987	United States public health service tuberculosis therapy Trial 21: preliminary results of an evaluation of a Combination tablet of isoniazid, rifampin and pyrazinamide	460	Technical 2nd, Standard care 2nd
Gross, 2009	Modified Directly Observed Antiretroviral Therapy Compared with Self-Administered Therapy in Treatment-Naïve HIV-1 Infected Patients: A Randomized Trial	243	Technical 2nd, Standard care 2nd
Gross, 2015	Partner-Focused Adherence Intervention for Second-line Antiretroviral Therapy: A Multinational Randomized Trial (ACTG A5234)	257	Standard care 2nd, Educational + Attitudinal + Technical 2nd
Holstad, 2012	Motivational Groups Support Adherence to Antiretroviral Therapy and use of Risk Reduction Behaviors in HIV Positive Nigerian Women: A Pilot Study	48	Educational 2nd, Attitudinal 2nd
Holzemer, 2006	Testing a Nurse-Tailored HIV Medication Adherence Intervention	180	Standard care 2nd, Educational + Attitudinal 2nd
Ingersoll, 2011	A Pilot Randomized Clinical Trial of Two Medication Adherence and Drug Use Interventions For HIV+ Crack Cocaine Users*	42	Educational 2nd, Attitudinal 2nd
Jarab, 2012	Randomized Controlled Trial of Clinical Pharmacy Management of Patients with Type 2 Diabetes in an Outpatient Diabetes Clinic in Jordan	171	Educational 2nd, Standard care 2nd
Johnson, 2011	Improving Coping Skills for Self-management of Treatment Side Effects Can Reduce Antiretroviral Medication Nonadherence among People Living with HIV	249	Standard care 2nd, Educational + Attitudinal 2nd
Joost, 2014	Intensified pharmaceutical care is improving immunosuppressive medication adherence in kidney transplant recipients during the first post-transplant year: a quasi-experimental study	74	Standard care 2nd, Educational + Technical 2nd
Katon, 1996	A Multifaceted Intervention to Improve Treatment of Depression in Primary Care	153	Standard care 2nd, Educational + Attitudinal 2nd
Kelly, 1990	Medication Compliance and Health Education Among Outpatients With Chronic Mental Disorders	418	Educational 2nd, Standard care 2nd
Klang, 2015	Community pharmacists' support improves antidepressant adherence in the community	12919	Technical 2nd, Standard care 2nd
Koenig, 2008	Randomized Controlled Trial of an Intervention to Prevent Adherence Failure Among HIV-Infected Patients Initiating Antiretroviral Therapy	226	Standard care 2nd, Educational + Attitudinal + Technical 2nd

Konkle-Parker, 2012	Pilot testing of an HIV medication adherence intervention in a public clinic in the Deep South	36	Standard care 2nd, Attitudinal 2nd
Konkle-Parker, 2014	"Effects of an Intervention Addressing Information, Motivation, and Behavioral Skills on HIV Care Adherence in a Southern Clinic Cohort"	100	Standard care 2nd, Educational + Attitudinal + Technical 2nd
Kopelowicz, 2003	Disease Management in Latinos With Schizophrenia: A Family-Assisted, Skills Training Approach	92	Standard care 2nd, Educational + Attitudinal 2nd
Kronish, 2012	The Effect of Enhanced Depression Care on Adherence to Risk Reducing Behaviors after Acute Coronary Syndromes: Findings from the COPES Trial	157	Standard care 2nd, Attitudinal 2nd
Lee, 1996	Assessing Medication Adherence by Pill Count and Electronic Monitoring in the African American Shdy of Kidney Disease and Hypertension (AASK) Pilot Study	313	Technical 2nd, Standard care 2nd
Levin, 2006	A Randomized Trial of Educational Materials, Pillboxes, and Mailings to Improve Adherence with Antiretroviral Therapy in an Inner City HIV Clinic	49	Standard care 2nd, Educational + Technical 2nd
Levine, 1979	Health Education for Hypertensive Patients	325	Standard care 2nd, Educational + Attitudinal 2nd
Lopez Cabezas, 2006	Randomized clinical trial of a postdischarge pharmaceutical care program vs. regular follow-up in patients with heart failure	74	Educational 2nd, Standard care 2nd
Magid, 2011	A Multimodal Blood Pressure Control Intervention in 3 Healthcare Systems	283	Educational 2nd, Educational + Technical 2nd
Marquez Contreas, 2004	Effectiveness of an intervention to provide information to patients with hypertension as short text messages and reminders sent to their mobile phone (HTA-Alert)	67	Standard care 2nd, Educational + Technical 2nd
Marquez-Contreras, 2004	Effectiveness of an Intervention to Provide Information to Patients With Hypertension as Short Text Messages of Reminders Sent to Their Mobile Phone (HTA-Alert)	67	Educational 2nd, Standard care 2nd
Marquez-Contreras, 2005	Efficacy of telephone and mail intervention in patient compliance with antihypertensive drugs in hypertension. ETECUM-HTA study	538	Technical 2nd, Educational 2nd, Standard care 2nd
Marquez-Contreras, 2007	Therapy compliance in cases of hyperlipaemia, as measured through electronic monitors. Is a reminder calendar to avoid forgetfulness effective?	220	Technical 2nd, Standard care 2nd
Matsumura, 2012	Does a Combination Pill of Antihypertensive Drugs Improve Medication Adherence in Japanese?	207	Technical 2nd, Standard care 2nd

Mbuagbaw, 2012	Mobile phone text messages for improving adherence to antiretroviral therapy (ART): an individual patient data meta-analysis of randomised trials	200	Technical 2nd, Standard care 2nd
McKenney, 1973	The Effect of Clinical Pharmacy Services on Patients with Essential Hypertension	49	Educational 2nd, Standard care 2nd
McKinstry, 2013	Telemonitoring based service redesign for the management of uncontrolled hypertension: multicentre randomised controlled trial	401	Technical 2nd, Standard care 2nd
Mckenney, 1978	Effect of Pharmacist Drug Monitoring and Patient Education on Hypertensive Patients	135	Educational 2nd, Standard care 2nd
Mehos, 2000	Effect of Pharmacist Intervention and Initiation of Home Blood Pressure Monitoring in Patients with Uncontrolled Hypertension	36	Educational 2nd, Educational + Technical 2nd
Mehuys, 2008	Effectiveness of pharmacist intervention for asthma control improvement	150	Educational 2nd, Standard care 2nd
Mols, 2015	Visualization of Coronary Artery Calcification: Influence on Risk Modification	189	Educational 2nd, Standard care 2nd
Montori, 2011	Use of a Decision Aid to Improve Treatment Decisions in Osteoporosis: The Osteoporosis Choice Randomized Trial	100	Educational 2nd, Standard care 2nd
Moss, 2010	Impact of a patient-support program on mesalamine adherence in patients with ulcerative colitis — A prospective study	62	Standard care 2nd, Educational + Attitudinal 2nd
Nachega, 2010	Randomized Controlled Trial of Trained Patient-Nominated Treatment Supporters Providing Partial Directly Observed Antiretroviral Therapy	274	Standard care 2nd, Educational + Technical 2nd
Nazareth, 2001	A pharmacy discharge plan for hospitalized elderly patients – a randomized controlled trial	362	Standard care 2nd, Educational + Attitudinal 2nd
Nunes, 2006	Behavioral Therapy to Augment Oral Naltrexone for Opioid Dependence: A Ceiling on Effectiveness?	69	Educational 2nd, Attitudinal + Rewards 2nd
Ostbring, 2014	Medication beliefs and self-reported adherence-results of a pharmacist's consultation: a pilot study	21	Standard care 2nd, Attitudinal 2nd
Parsons, 2007	Motivational Interviewing and Cognitive-Behavioral Intervention to Improve HIV Medication Adherence Among Hazardous Drinkers: A Randomized Controlled Trial	115	Educational 2nd, Attitudinal 2nd
Pearson, 2007	Randomized Control Trial of Peer-Delivered, Modified Directly Observed Therapy for HAART in Mozambique	350	Standard care 2nd,

			Educational + Technical 2nd
Petrie, 2012	A text message programme designed to modify patients' illness and treatment beliefs improves self-reported adherence to asthma preventer medication	103	Educational 2nd, Standard care 2nd
Pladevall, 2010	A multi-center cluster-randomized trial of a multifactorial Intervention to improve antihypertensive Medication adherence and blood pressure control Among patients at high cardiovascular risk (the Com99 study)*	875	Standard care 2nd, Educational + Attitudinal 2nd
Pradier, 2003	Efficacy of an Educational and Counseling Intervention on Adherence to Highly Active Antiretroviral Therapy: French Prospective	202	Standard care 2nd, Educational + Attitudinal 2nd
Purcell, 2007	Results From a Randomized Controlled Trial of a Peer-Mentoring Intervention to Reduce HIV Transmission and Increase Access to Care and Adherence	405	Educational 2nd, Attitudinal 2nd
Pyne, 2011	Effectiveness of Collaborative Care for Depression in Human Immunodeficiency Virus Clinics	194	Standard care 2nd, Educational + Technical 2nd
Ramirez-Garcia & Cote, 2012	An Individualized Intervention to Foster Optimal Antiretroviral Treatment-Taking Behavior Among Persons Living With HIV: A Pilot Randomized Controlled Trial	44	Standard care 2nd, Educational + Attitudinal 2nd
Rawlings, 2003	Impact of an Educational Program on Efficacy and Adherence With a Twice-Daily Lamivudine/Zidovudine/Abacavir Regimen in Underrepresented HIV-Infected Patients	195	Educational 2nd, Standard care 2nd
Rehder, 1980	Improving medication compliance by counseling and special prescription container	100	Technical 2nd, Educational 2nd, Standard care 2nd, Educational + Technical 2nd
Rinfret, 2013	Telephone contact to improve adherence to dual antiplatelet therapy after drug-eluting stent implantation	300	Educational 2nd, Standard care 2nd
Rubio-Valera, 2013	Evaluation of a pharmacist intervention on patients initiating pharmacological treatment for depression: A randomized controlled superiority trial	179	Educational 2nd, Standard care 2nd
Sackett, 1975	Randomised clinical trial of strategies for improving medication compliance in primary hypertension	230	Educational 2nd, Standard care 2nd
Safren, 2003	Use of an on-line pager system to increase adherence to antiretroviral medications	60	Technical 2nd, Standard care 2nd
Samet, 2005	A randomized controlled trial to enhance antiretroviral therapy adherence in patients with a history of alcohol problems	138	Standard care 2nd, Educational +

			Attitudinal + Technical 2nd
Saunders, 1991	A Randomized Controlled Trial of Compliance Improving Strategies in Soweto Hypertensives	115	Educational 2nd, Educational + Technical 2nd
Schaffer and Tian, 2004	Promoting Adherence Effects of Theory-Based Asthma Education	70	Educational 2nd, Standard care 2nd
Selke, 2010	Task-Shifting of Antiretroviral Delivery From Health Care Workers to Persons Living With HIV/AIDS: Clinical Outcomes of a Community-Based Program in Kenya	208	Educational 2nd, Standard care 2nd
Sherrard, 2009	Using Technology to Create a Medication Safety Net for Cardiac Surgery Patients: A Nurse-Led Randomized Control Trial	331	Technical 2nd, Standard care 2nd
Simon, 2011	Randomized Trial of Depression Follow-Up Care by Online Messaging	208	Technical 2nd, Standard care 2nd
Simoni, 2013	A Preliminary RCT of CBT-AD for Adherence and Depression among HIV-Positive Latinos on the U.S. – Mexico Border: The Nuevo Día Study	40	Standard care 2nd, Educational + Attitudinal + Technical 2nd
Sookaneknun, 2004	Pharmacist Involvement in Primary Care Improves Hypertensive Patient Clinical Outcomes	235	Standard care 2nd, Educational + Technical 2nd
Stacy, 2009	Incorporating Tailored Interactive Patient Solutions Using Interactive Voice Response Technology to Improve Statin Adherence: Results of a Randomized Clinical Trial in a Managed Care Setting	497	Standard care 2nd, Educational + Technical 2nd
Stewart, 2014	A multifaceted pharmacist intervention to improve antihypertensive adherence: a cluster-randomized, controlled trial (HAPPy trial)	354	Standard care 2nd, Educational + Attitudinal + Technical 2nd
Taiwo, 2010	Assessing the Viorologic and Adherence Benefits of Patient-Selected HIV Treatment Partners in a Resource-limited Setting	499	Technical 2nd, Standard care 2nd
Tsuyuki, 2004	A Multicenter Disease Management Program for Hospitalized Patients With Heart Failure	276	Standard care 2nd, Educational + Technical 2nd
Tuldra, 2000	Prospective Randomized Two-Arm Controlled Study To Determine the Efficacy of a Specific Intervention To Improve Long-Term Adherence to Highly Active Antiretroviral Therapy	116	Standard care 2nd, Attitudinal 2nd
Wagner, 2006	Cognitive-behavioral intervention to enhance adherence to antiretroviral therapy: a randomized controlled trial (CCTG 578)	199	Standard care 2nd, Attitudinal 2nd

Wagner, 2013	Pilot Controlled Trial of the Adherence Readiness Program: An Intervention to Assess and Sustain HIV Antiretroviral Adherence Readiness	60	Standard care 2nd, Educational + Attitudinal 2nd
Wakefield, 2009	Outcomes of a home telehealth intervention for patients with heart failure	89	Educational 2nd, Standard care 2nd
Wald, 2014	Randomised Trial of Text Messaging on Adherence to Cardiovascular Preventive treatment (INTERACT Trial)	301	Technical 2nd, Standard care 2nd
Williams, 2006	Home Visits to Improve Adherence to Highly Active Antiretroviral Therapy: A Randomized Controlled Trial	171	Standard care 2nd, Educational + Attitudinal 2nd
Williams, 2014	Efficacy of an Evidence-Based ARV Adherence Intervention in China	110	Standard care 2nd, Educational + Attitudinal 2nd
Wohl, 2006	A Randomized Trial of Directly Administered Antiretroviral Therapy and Adherence Case Management Intervention	96	Technical 2nd, Educational 2nd, Standard care 2nd
Wong, 2013	Effectiveness of a Pharmacist-Led Drug Counseling on Enhancing Antihypertensive Adherence and Blood Pressure Control: A Randomized Controlled Trial	231	Standard care 2nd, Educational + Technical 2nd
Wong, 2017	A pharmacy management service for adults with asthma: a cluster randomised controlled trial	157	Educational 2nd, Standard care 2nd
Zaretsky, 2008	Is Cognitive-Behavioural Therapy More Effective Than Psychoeducation in Bipolar Disorder?	79	Educational 2nd, Educational + Attitudinal 2nd
van Gent, 1991	Psychoeducation of partners of bipolar-manic patients	39	Educational 2nd, Standard care 2nd

7-9 months

Study ID	Title	Study size	Interventions
Asplund, 1984	Patients compliance in hypertension-the importance of number of tablets	160	Technical 3rd, Standard care 3rd
Brown, 1997	Moderate Dose, Three-Drug Therapy With Niacin, Lovastatin, and Colestipol to Reduce Low-Density Lipoprotein Cholesterol ò100 mg/dl in Patients With Hyperlipidemia and Coronary Artery Disease	29	Technical 3rd, Standard care 3rd
Capoccia, 2004	Randomized trial of pharmacist interventions to improve depression care and outcomes in primary care	74	Educational + Technical 3rd, Standard care 3rd
Castellano, 2014	A Polypill Strategy to Improve Adherence Results From the FOCUS Project	695	Technical 3rd, Standard care 3rd
Dusing, 2009	Impact of supportive measures on drug adherence in patients with essential hypertension treated with valsartan: the randomized, open-label, parallel group study VALIDATE	202	Educational + Technical 3rd, Standard care 3rd
Johnson, 2011	Improving Coping Skills for Self-management of Treatment Side Effects Can Reduce Antiretroviral Medication Nonadherence among People Living with HIV	249	Educational + Attitudinal 3rd, Standard care 3rd
Katon, 1996	A Multifaceted Intervention to Improve Treatment of Depression in Primary Care	153	Educational + Attitudinal 3rd, Standard care 3rd
Kronish, 2012	The Effect of Enhanced Depression Care on Adherence to Risk Reducing Behaviors after Acute Coronary Syndromes: Findings from the COPES Trial	157	Attitudinal 3rd, Standard care 3rd
Margolin, 2003	A Randomized Clinical Trial of a Manual-Guided Risk Reduction Intervention for HIV-Positive Injection Drug Users	69	Educational + Attitudinal 3rd, Educational 3rd
Peterson, 1984	A Randomised Trial of Strategies to Improve Patient Compliance with Anticonvulsant Therapy	53	Educational + Technical 3rd, Standard care 3rd
Powell, 1995	Failure of educational videotapes to improve medication compliance in a health maintenance organization	4246	Educational 3rd, Standard care 3rd
Rathburn, 2005	Impact of an Adherence Clinic on Behavioral Outcomes and Virologic Response in the Treatment of HIV Infection: A Prospective, Randomized, Controlled Pilot Study	33	Educational + Technical 3rd, Standard care 3rd
Simoni, 2009	An RCT of Peer Support and Pager Messaging to Promote Antiretroviral Therapy Adherence and Clinical	224	Educational + Attitudinal + Technical 3rd,

	Outcomes among Adults Initiating or Modifying Therapy in Seattle, WA, USA		Educational + Attitudinal 3rd, Educational + Technical 3rd, Standard care 3rd
Simoni, 2013	"A Preliminary RCT of CBT-AD for Adherence and Depression among HIV-Positive Latinos on the U.S. – Mexico Border: The Nuevo Día Study"	40	Educational + Attitudinal + Technical 3rd, Standard care 3rd
Smith, 2008	A Randomized Trial of Direct-to-Patient Communication to Enhance Adherence to B-Blocker Therapy Following Myocardial Infarction	888	Educational 3rd, Standard care 3rd
Velligan, 2008	The Use of Individually Tailored Environmental Supports to Improve Medication Adherence and Outcomes in Schizophrenia	61	Attitudinal 3rd, Standard care 3rd
Williams, 2006	Home Visits to Improve Adherence to Highly Active Antiretroviral Therapy: A Randomized Controlled Trial	171	Educational + Attitudinal 3rd, Standard care 3rd
Wu, 2012	Effect of a Medication-Taking Behavior Feedback, Theory-Based Intervention on Outcomes in Patients with Heart Failure	82	Educational + Attitudinal + Technical 3rd, Attitudinal 3rd, Standard care 3rd

≥10 months

Study ID	Title	Study size	Interventions
Antonicelli, 2010	Impact of Home Patient Telemonitoring on Use of ß-Blockers in Congestive Heart Failure	57	Educational + Technical 4th, Standard care 4th
Ball, 2006	A Randomized Controlled Trial of Cognitive Therapy for Bipolar Disorder: Focus on Long-Term Change	52	Attitudinal 4th, Standard care 4th
Boyle, 2008	Randomization to Once-Daily Stavudine Extended Release/Lamivudine/Efavirenz Versus a More Frequent Regimen Improves Adherence While Maintaining Viral Suppression	300	Technical 4th, Standard care 4th
Brankin, 2006	The impact of dosing frequency on compliance and persistence with bisphosphonates among postmenopausal women in the UK: evidence from three databases	15330	Technical 4th, Standard care 4th
Broekhuizen, 2012	Can Multiple Lifestyle Behaviours Be Improved in People with Familial Hypercholesterolemia? Results of a Parallel Randomised Controlled Trial	224	Educational + Attitudinal 4th, Standard care 4th
Capoccia, 2004	Randomized trial of pharmacist interventions to improve depression care and outcomes in primary care	74	Educational + Technical 4th, Standard care 4th
Chang, 2010	Effect of Peer Health Workers on AIDS Care in Rakai, Uganda: A Cluster-Randomized Trial	1203	Educational + Technical 4th, Standard care 4th
Choudhry, 2011	Full Coverage for Preventive Medications after Myocardial Infarction	5855	Rewards 4th, Standard care 4th
Clowes, 2004	The Impact of Monitoring on Adherence and Persistence with Antiresorptive Treatment for Postmenopausal Osteoporosis: A Randomized Controlled Trial	48	Technical 4th, Standard care 4th
Collier, 2005	A Randomized Study of Serial Telephone Call Support to Increase Adherence and Thereby Improve Virologic Outcome in Persons Initiating Antiretroviral Therapy	101	Educational + Attitudinal 4th, Standard care 4th
Cramer, 2005	Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis	2741	Technical 4th, Standard care 4th
Cramer, 2006	The Effect of Dosing Frequency on Compliance and Persistence with Bisphosphonate Therapy in Postmenopausal Women: A Comparison of Studies in the United States, the United Kingdom, and France	15640	Technical 4th, Standard care 4th

Delmas, 2007	Effect of Monitoring Bone Turnover Markers on Persistence with Risedronate Treatment of Postmenopausal Osteoporosis	2302	Technical 4th, Standard care 4th
Derose, 2013	Automated Outreach to Increase Primary Adherence to Cholesterol-Lowering Medications	5216	Educational + Technical 4th, Standard care 4th
Edworthy, 2007	Effects of an enhanced secondary prevention program for patients with heart disease: A prospective randomized trial	2643	Educational 4th, Standard care 4th
Eron, 2004	Once-Daily versus Twice-Daily Lopinavir/Ritonavir in Antiretroviral-Naive HIV-Positive Patients: A 48-Week Randomized Clinical Trial	38	Technical 4th, Standard care 4th
Eussen, 2010	A Pharmaceutical Care Program to Improve Adherence to Statin Therapy: A Randomized Controlled Trial	899	Educational 4th, Standard care 4th
Falces, 2008	[An educative intervention to improve treatment compliance and to prevent readmissions of elderly patients with heart failure]	103	Educational 4th, Standard care 4th
Gallant, 2006	Tenofovir DF, Emtricitabine, and Efavirenz vs. Zidovudine, Lamivudine, and Efavirenz for HIV	509	Technical 4th, Standard care 4th
Gamble, 2011	A study of a multi-level intervention to improve non-adherence in difficult to control asthma	18	Educational + Attitudinal 4th, Standard care 4th
Glanz, 2012	Impact of a Health Communication Intervention to Improve Glaucoma Treatment Adherence: Results of the I-SIGHT Trial	302	Educational + Technical 4th, Standard care 4th
Goswami, 2013	Impact of an integrated intervention program on atorvastatin adherence: a randomized controlled trial	208	Educational 4th, Standard care 4th
Gross, 2013	Managed Problem Solving for Antiretroviral Therapy Adherence: A Randomized Trial	180	Educational + Attitudinal + Technical 4th, Standard care 4th
Gurjal, 2014	Impact of community pharmacist intervention discussing patients' beliefs to improve medication adherence	200	Attitudinal 4th, Standard care 4th
Hadji, 2013	The Patient's Anastrozole Compliance to Therapy (PACT) Program: a randomized, in-practice study on the impact of a standardized information program on persistence and compliance to adjuvant endocrine therapy in postmenopausal women with early breast cancer†	2800	Educational + Technical 4th, Standard care 4th
Hawkins, 1979	Evaluation of a clinical pharmacist in caring for hypertensive and diabetic patients	137	Educational 4th, Standard care 4th

Hirsch, 2009	Evaluation of the First Year of a Pilot Program in Community Pharmacy: HIV/AIDS Medication Therapy Management for Medi-Cal Beneficiaries	7018	Educational 4th, Standard care 4th
Hirsch, 2011	Antiretroviral Therapy Adherence, Medication Use, and Health Care Costs During 3 Years of a Community Pharmacy Medication Therapy Management Program for Medi-Cal Beneficiaries with HIV/AIDS	2234	Educational + Technical 4th, Standard care 4th
Ho, 2014	Multifaceted Intervention to Improve Medication Adherence and Secondary Prevention Measures After Acute Coronary Syndrome Hospital Discharge A Randomized Clinical Trial	241	Educational + Technical 4th, Standard care 4th
Homer, 2009	Providing patients with information about disease-modifying antirheumatic drugs: Individually or in groups? A pilot randomized controlled trial comparing adherence and satisfaction	62	Educational 4th, Educational + Technical 4th
Hornnes, 2011	Blood Pressure 1 Year after Stroke: The Need to Optimize Secondary Prevention	293	Educational + Technical 4th, Standard care 4th
Hunt, 2008	A Randomized Controlled Trial of Team-Based Care: Impact of Physician-Pharmacist Collaboration on Uncontrolled Hypertension	272	Educational + Technical 4th, Standard care 4th
Johnson, 2011	Improving Coping Skills for Self-management of Treatment Side Effects Can Reduce Antiretroviral Medication Nonadherence among People Living with HIV	249	Educational + Attitudinal 4th, Standard care 4th
Joost, 2014	Intensified pharmaceutical care is improving immunosuppressive medication adherence in kidney transplant recipients during the first post-transplant year: a quasi-experimental study	74	Educational + Technical 4th, Standard care 4th
Kellaway, 1979	The effect of counselling on compliance-failure in patient drug therapy	757	Educational + Technical 4th, Standard care 4th
Kiweewa, 2013	Noninferiority of a Task-Shifting HIV Care and Treatment Model Using Peer Counselors and Nurses Among Ugandan Women Initiated on ART: Evidence From a Randomized Trial	85	Educational 4th, Standard care 4th
Konkle-Parker, 2014	"Effects of an Intervention Addressing Information, Motivation, and Behavioral Skills on HIV Care Adherence in a Southern Clinic Cohort"	100	Educational + Attitudinal + Technical 4th, Standard care 4th
Kooy, 2013	Does the use of an electronic reminder device with or without counseling improve adherence to lipid-lowering treatment? The results of a randomized controlled trial	381	Technical 4th, Attitudinal + Technical 4th, Standard care 4th

Lam, 2003	A Randomized Controlled Study of Cognitive Therapy for Relapse Prevention for Bipolar Affective Disorder	103	Attitudinal 4th, Standard care 4th
Lester, 2010	Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial	538	Technical 4th, Standard care 4th
Lopez Cabezas, 2006	Randomized clinical trial of a postdischarge pharmaceutical care program vs. regular follow-up in patients with heart failure	63	Educational 4th, Standard care 4th
Lucas, 2013	Directly Administered Antiretroviral Therapy for HIVInfected Individuals in Opioid Treatment Programs: Results from a Randomized Clinical Trial	107	Technical 4th, Standard care 4th
Malotte, 2001	Incentives vs Outreach Workers for Latent Tuberculosis Treatment in Drug Users	163	Rewards + Technical 4th, Technical 4th
Markopoulous, 2015	Does patient education work in breast cancer? Final results from the global CARIATIDE study	2757	Educational 4th, Standard care 4th
Molina, 2007	A Lopinavir/Ritonavir-Based Once-Daily Regimen Results in Better Compliance and Is Non-inferior to a Twice-Daily Regimen Through 96 Weeks	190	Technical 4th, Standard care 4th
Morisky, 1985	Evaluation of family health education to build social support for long-term control of high blood pressure.	290	Educational 4th, Standard care 4th
Morisky, 1990	A Patient Education Program to Improve Adherence Rates with Antituberculosis Drug Regimens	88	Educational + Attitudinal + Rewards 4th, Standard care 4th
Moshkovska, 2011	Impact of a Tailored Patient Preference Intervention in Adherence to 5-Aminosalicylic Acid Medication in Ulcerative Colitis: Results from an Exploratory Randomized Controlled Trial	71	Educational + Attitudinal + Technical 4th, Standard care 4th
Mugusi, 2009	Enhancing adherence to antiretroviral therapy at the HIV clinic in resource constrained countries; the Tanzanian experience	621	Technical 4th, Educational + Technical 4th, Standard care 4th
Munoz, 2009	Community-based DOT-HAART Accompaniment in an Urban Resource-Poor Setting	120	Educational + Technical 4th, Standard care 4th
Nielson, 2010	Patient education in groups increases knowledge of osteoporosis and adherence to treatment: A two-year randomized controlled trial	300	Educational 4th, Standard care 4th
Ogedegbe, 2008	A Practice-based Trial of Motivational Interviewing and Adherence in Hypertensive 065African Americans	160	Attitudinal 4th, Standard care 4th

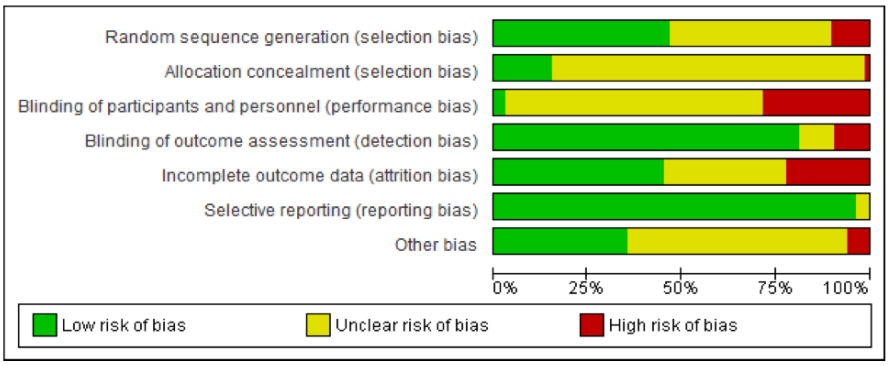
Ogedegbe, 2012	A Randomized Controlled Trial of Positive-Affect Intervention and Medication Adherence in Hypertensive African Americans	256	Educational 4th, Educational + Attitudinal 4th
Pagoto, 2013	Can attention control conditions have detrimental effects in behavioral medicine randomized trials?	235	Educational 4th, Standard care 4th
Palacio, 2015	Can Phone-Based Motivational Interviewing Improve Medication Adherence to Antiplatelet Medications After a Coronary Stent Among Racial Minorities? A Randomized Trial	339	Attitudinal 4th, Educational 4th
Pearson, 2007	Randomized Control Trial of Peer-Delivered, Modified Directly Observed Therapy for HAART in Mozambique	350	Educational + Technical 4th, Standard care 4th
Piette, 2000	Do Automated Calls with Nurse Follow-up Improve Self-Care and Glycemic Control among Vulnerable Patients with Diabetes?	248	Educational + Technical 4th, Standard care 4th
Piette, 2001	Impact of Automated Calls With Nurse Follow-Up on Diabetes Treatment Outcomes in a Department of Veterans Affairs Health Care System A randomized controlled trial	272	Educational + Technical 4th, Standard care 4th
Pop-Eleches, 2011	Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders	428	Technical 4th, Standard care 4th
Purcell, 2007	Results From a Randomized Controlled Trial of a Peer-Mentoring Intervention to Reduce HIV Transmission and Increase Access to Care and Adherence	408	Attitudinal 4th, Educational 4th
Pyne, 2011	Effectiveness of Collaborative Care for Depression in Human Immunodeficiency Virus Clinics	178	Educational + Technical 4th, Standard care 4th
Rabenda, 2008a	Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women	29157	Technical 4th, Standard care 4th
Rabenda, 2008b	Low Incidence of Anti-Osteoporosis Treatment After Hip Fracture	306	Technical 4th, Standard care 4th
Reinares, 2008	Impact of caregiver group psychoeducation on the course and outcome of bipolar patients in remission: a randomized controlled trial	113	Educational + Attitudinal 4th, Standard care 4th
Reynolds, 2008	Telephone Support to Improve Antiretroviral Medication Adherence	109	Educational 4th, Educational + Attitudinal 4th

Rinfret, 2013	Telephone contact to improve adherence to dual antiplatelet therapy after drug-eluting stent implantation	300	Educational 4th, Standard care 4th
Sabin, 2010	Using Electronic Drug Monitor Feedback to Improve Adherence to Antiretroviral Therapy Among HIV-Positive Patients in China	64	Educational + Technical 4th, Standard care 4th
Sadik, 2005	Pharmaceutical care of patients with heart failure	208	Educational + Technical 4th, Standard care 4th
Samet, 2005	A randomized controlled trial to enhance antiretroviral therapy adherence in patients with a history of alcohol problems	94	Educational + Attitudinal + Technical 4th, Standard care 4th
Selke, 2010	Task-Shifting of Antiretroviral Delivery From Health Care Workers to Persons Living With HIV/AIDS: Clinical Outcomes of a Community-Based Program in Kenya	208	Educational 4th, Standard care 4th
Shet, 2014	Effect of mobile telephone reminders on treatment outcome in HIV: evidence from a randomised controlled trial in India	631	Technical 4th, Standard care 4th
Silveira, 2014	Randomized Controlled Trial to Evaluate the Impact of Pharmaceutical Care on Therapeutic Success in HIV-Infected Patients in Southern Brazil	332	Educational 4th, Standard care 4th
Soloman, 2012	Osteoporosis Telephonic Intervention to Improve Medication Adherence (OPTIMA): A Large Pragmatic Randomized Controlled Trial	2087	Attitudinal 4th, Educational 4th
Sosa, 2005	Abacavir and Lamivudine Fixed-Dose Combination Tablet	236	Technical 4th, Standard care 4th
Su and Pergn, 2002	Fixed-dose combination chemotherapy (Rifater®/Rifinah®) for active pulmonary tuberculosis in Taiwan: a two-year follow-up	52	Technical 4th, Standard care 4th
Taiwo, 2010	Assessing the Viorologic and Adherence Benefits of Patient-Selected HIV Treatment Partners in a Resource-limited Setting	499	Technical 4th, Standard care 4th
Taylor, 2003	Improving primary care in rural Alabama with a pharmacy initiative	69	Educational + Technical 4th, Standard care 4th
Thom, 2013	Effects of a Fixed-Dose Combination Strategy on Adherence and Risk Factors in Patients With or at High Risk of CVD The UMPIRE Randomized Clinical Trial	1860	Technical 4th, Standard care 4th
Tuldra, 2000	Prospective Randomized Two-Arm Controlled Study To Determine the Efficacy of a Specific Intervention To Improve Long-Term Adherence to Highly Active Antiretroviral Therapy	116	Attitudinal 4th, Standard care 4th

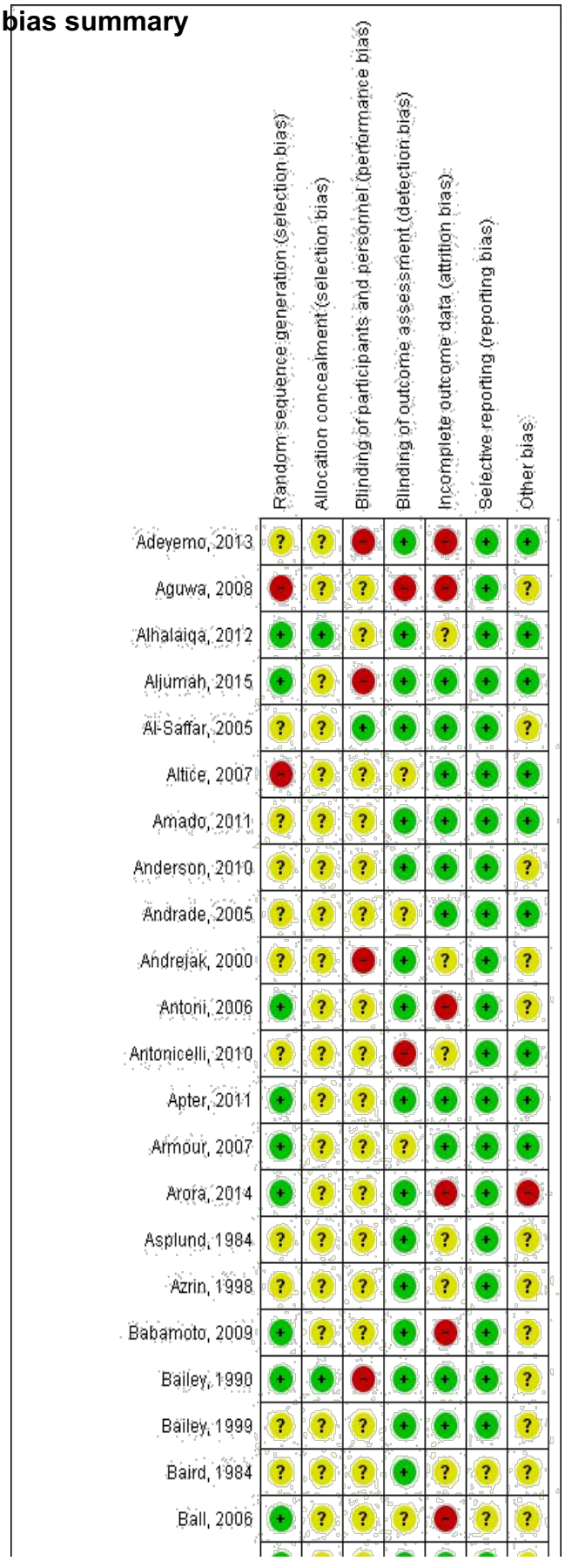
Valencia, 2008	A psychosocial skills training approach in Mexican out-patients with schizophrenia	82	Educational 4th, Standard care 4th
Varma, 1999	Pharmaceutical Care of Patients with Congestive Heart Failure: Interventions and Outcomes	49	Educational + Technical 4th, Standard care 4th
Velligan, 2008	The Use of Individually Tailored Environmental Supports to Improve Medication Adherence and Outcomes in Schizophrenia	61	Attitudinal 4th, Standard care 4th
Villeneuve, 2010	A cluster randomized controlled Trial to Evaluate an Ambulatory primary care Management program for patients with dyslipidemia: the TEAM study	225	Educational 4th, Standard care 4th
Vollmer, 2014	Improving Adherence to Cardiovascular Disease Medications With Information Technology	21752	Technical 4th, Educational + Technical 4th, Standard care 4th
Wagner, 2006	Cognitive-behavioral intervention to enhance adherence to antiretroviral therapy: a randomized controlled trial (CCTG 578)	199	Attitudinal 4th, Standard care 4th
Wang, 2011	Effects of pharmaceutical care interventions on blood pressure and medication adherence of patients with primary hypertension in China	59	Educational + Technical 4th, Standard care 4th
Weber, 2004	Effect of individual cognitive behaviour intervention on adherence to antiretroviral therapy: prospective randomized trial	60	Attitudinal 4th, Standard care 4th
Williams, 2006	Home Visits to Improve Adherence to Highly Active Antiretroviral Therapy: A Randomized Controlled Trial	171	Educational + Attitudinal 4th, Standard care 4th
Williams, 2014	Efficacy of an Evidence-Based ARV Adherence Intervention in China	110	Educational + Attitudinal 4th, Standard care 4th
Windsor, 1990	Evaluation of the Efficacy and Cost Effectiveness of Health Education Methods to Increase Medication Adherence among Adults with Asthma	267	Educational 4th, Standard care 4th
Xavier, 2016	"Community health worker-based intervention for adherence to drugs and lifestyle change after acute coronary syndrome: a multicentre, open, randomised controlled trial"	750	Educational + Technical 4th, Standard care 4th
Ziller, 2013	Influence of a patient information program on adherence and persistence with an aromatase inhibitor in breast cancer treatment - the COMPAS study	171	Educational 4th, Educational + Technical 4th, Standard care 4th

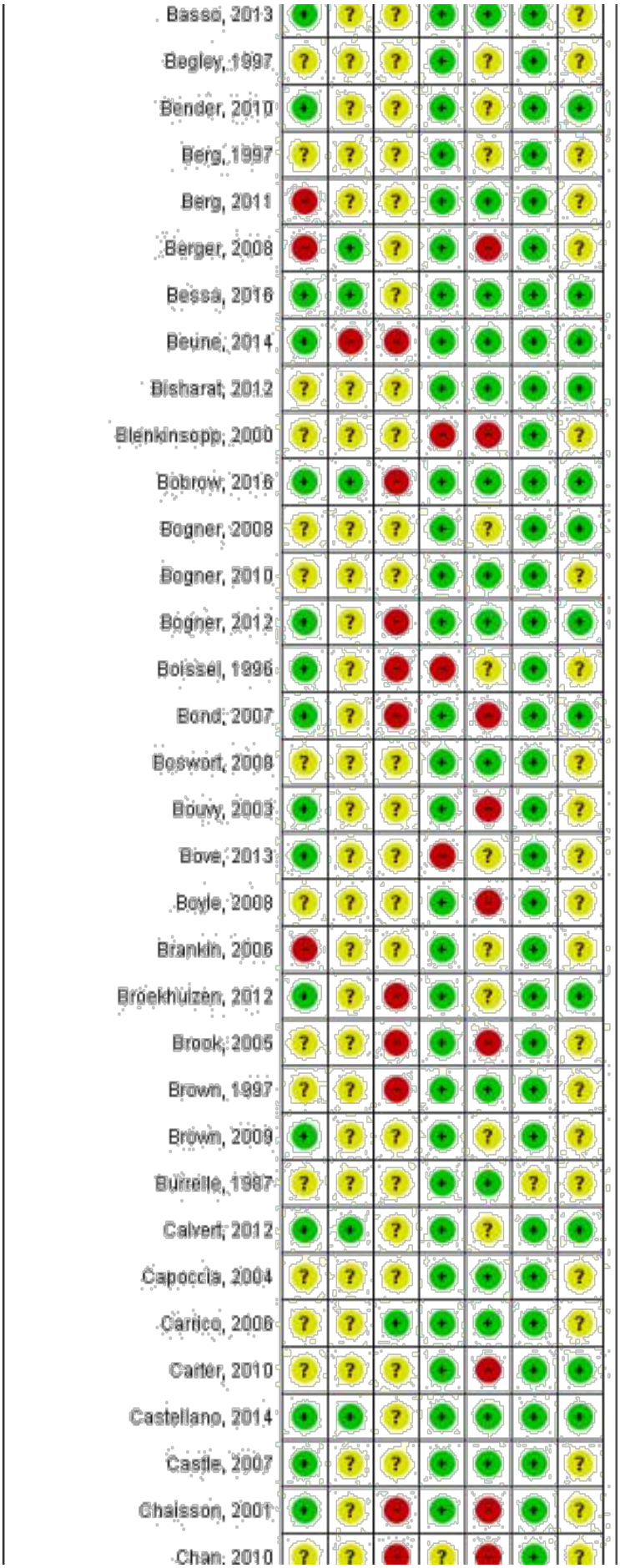
Zillich, 2012	Evaluation of Specialized Medication Packaging Combined With Medication Therapy Management: Adherence, Outcomes, and Costs Among Medicaid Patients	14621	Educational 4th, Standard care 4th
Zwikker, 2014	Effectiveness of a group-based intervention to change medication beliefs and improve medication adherence in patients with rheumatoid arthritis: A randomized controlled trial	123	Attitudinal 4th, Educational 4th

S1 Fig. Risk of bias graph



S3 Table. Risk of bias summary

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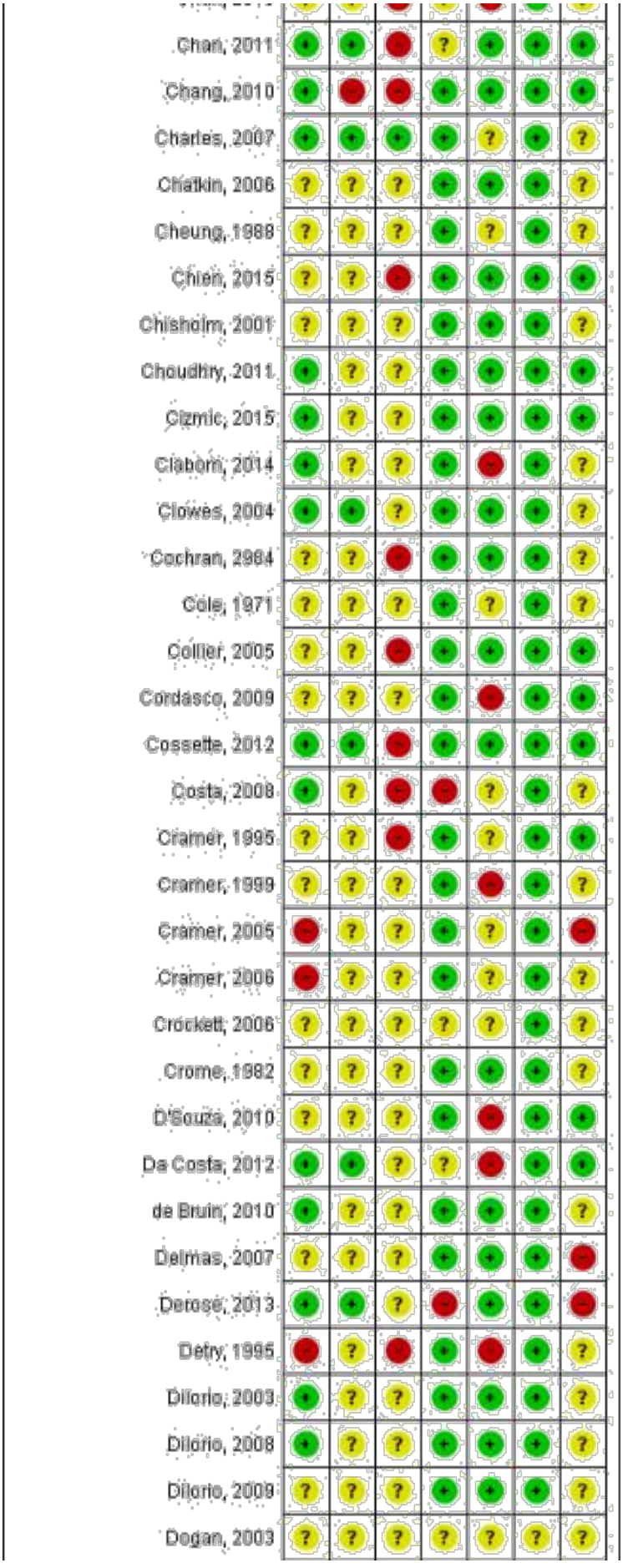
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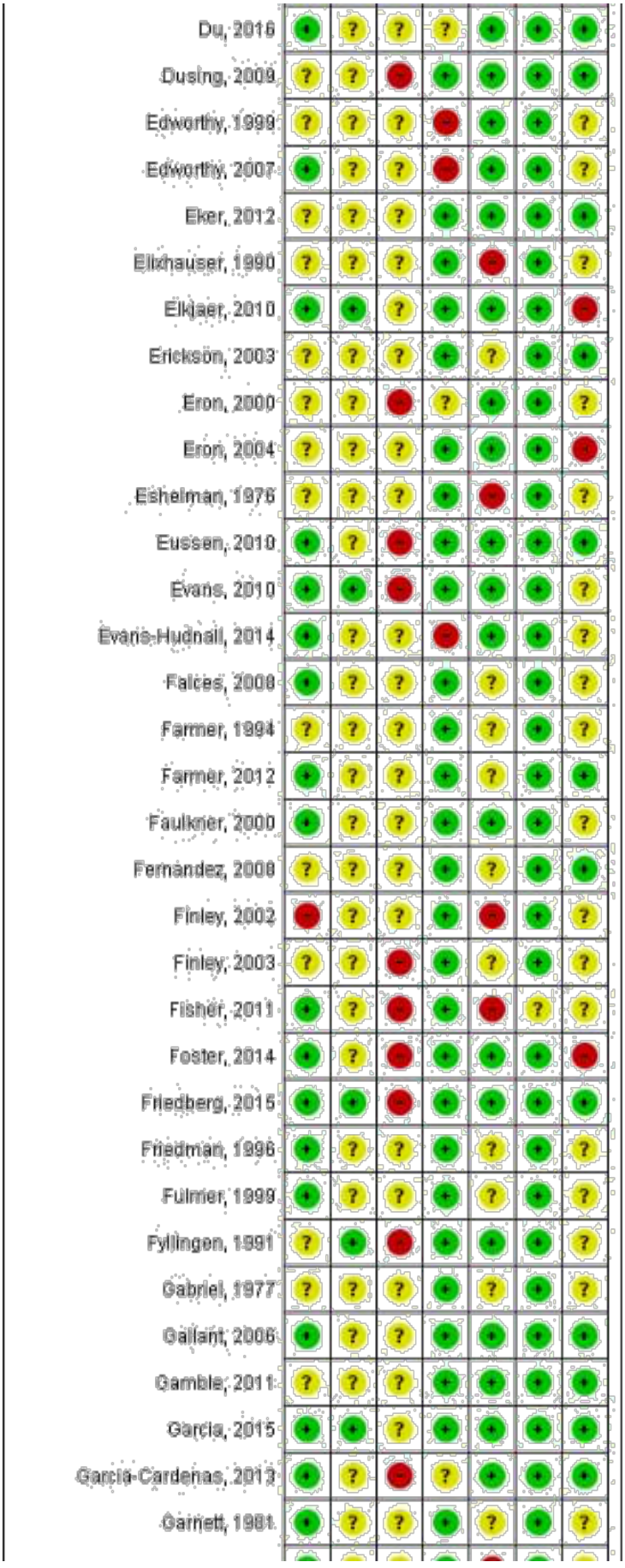
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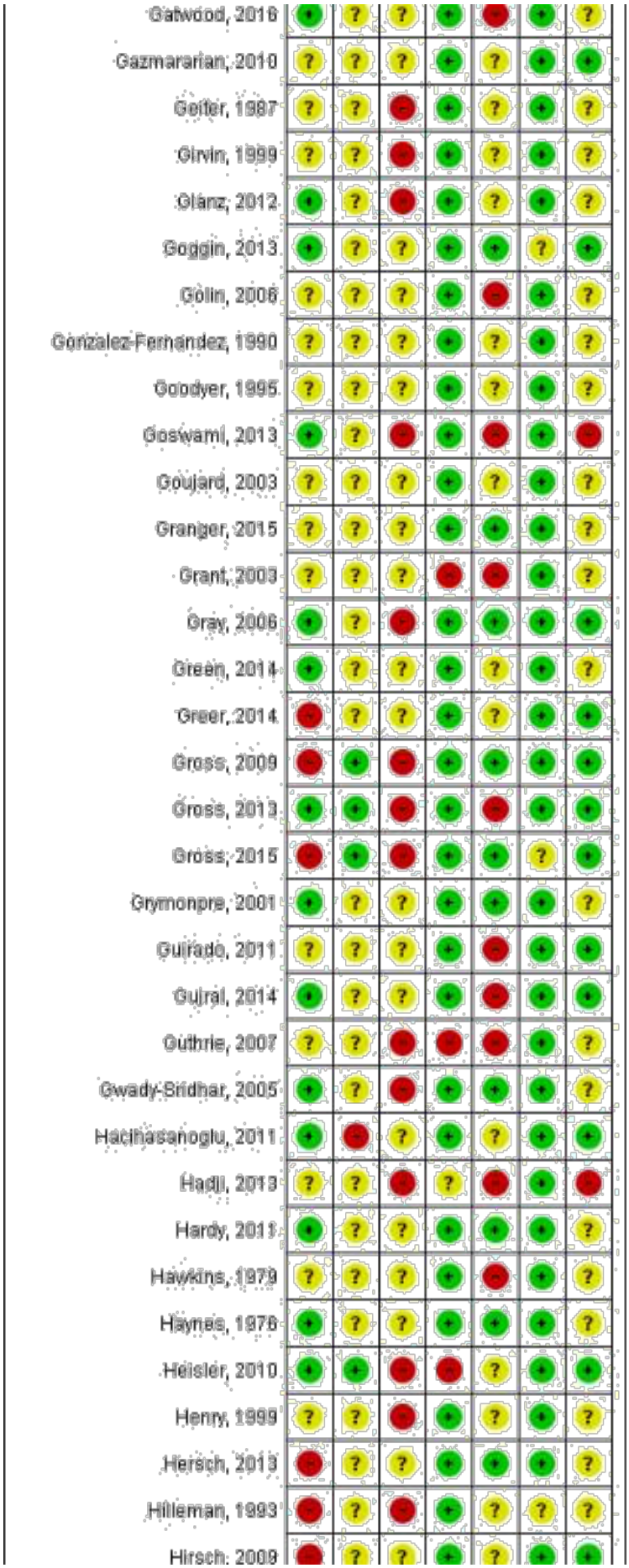
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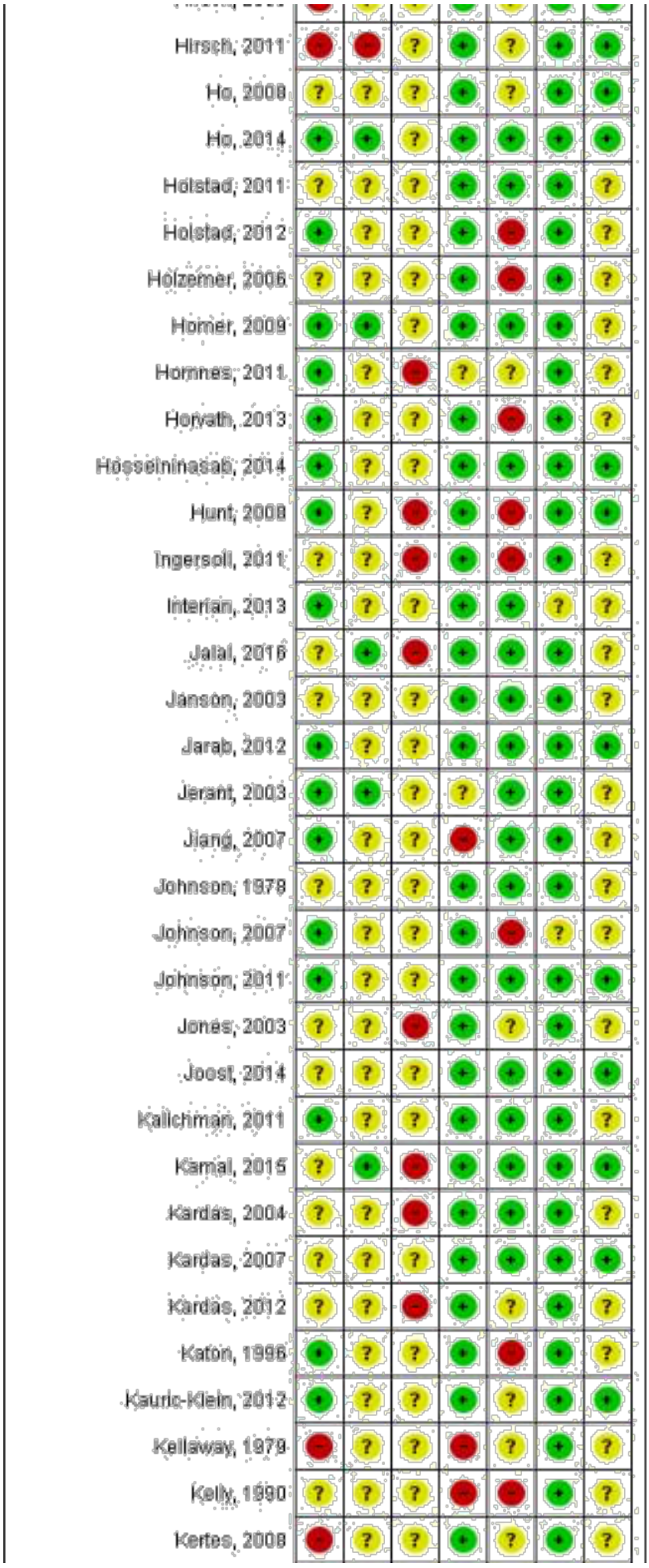
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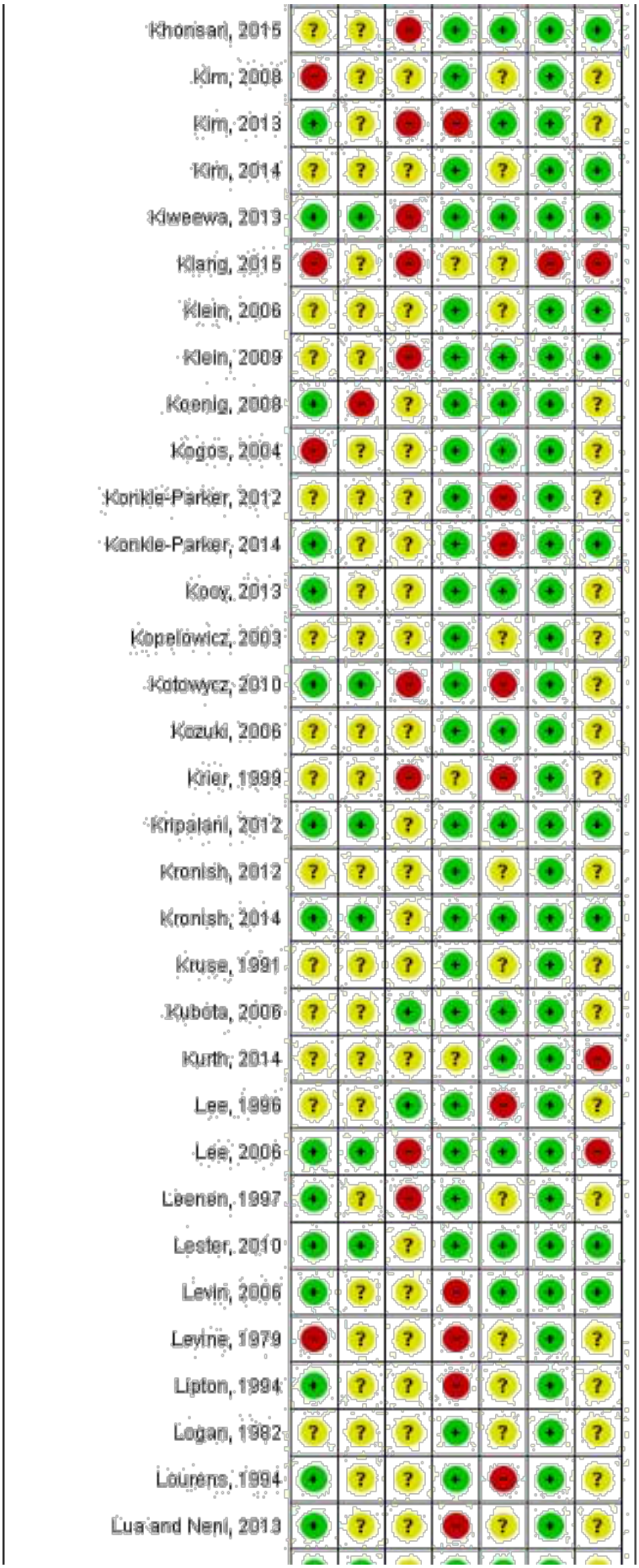
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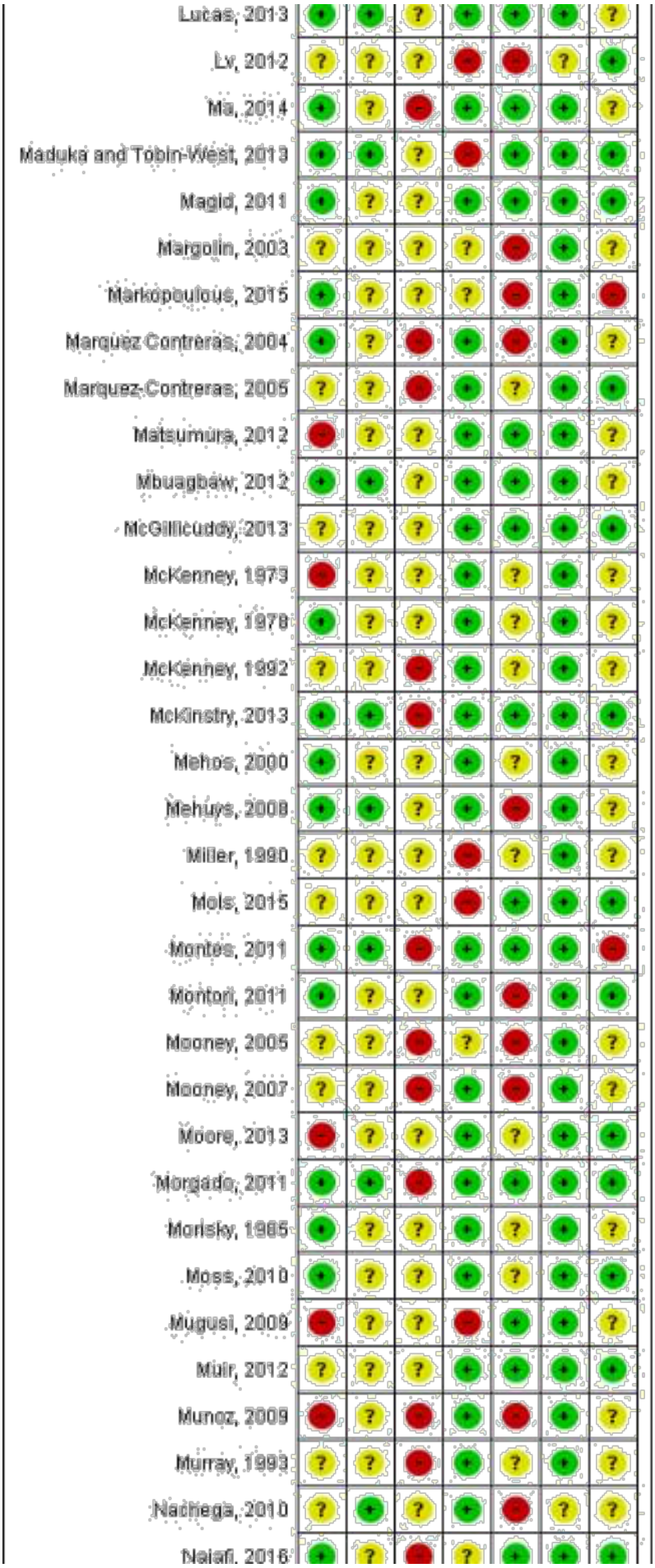
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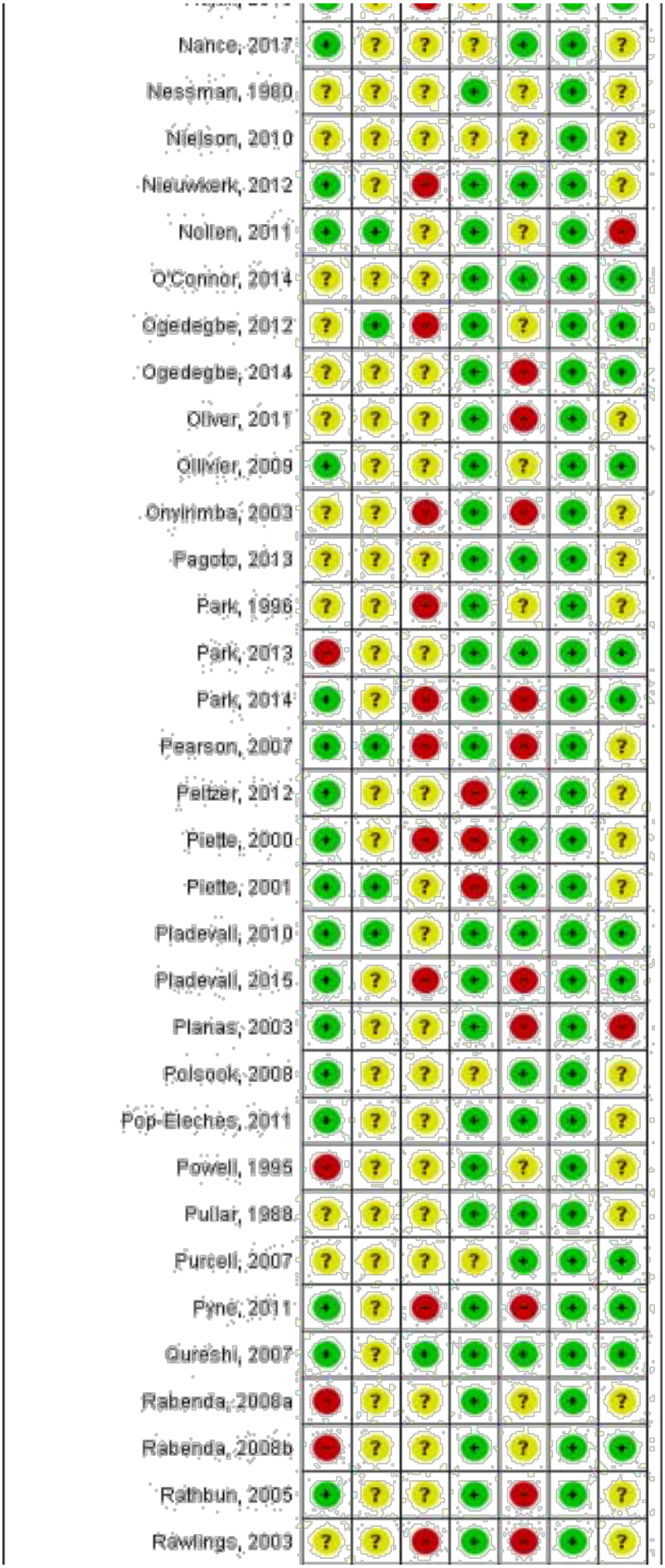
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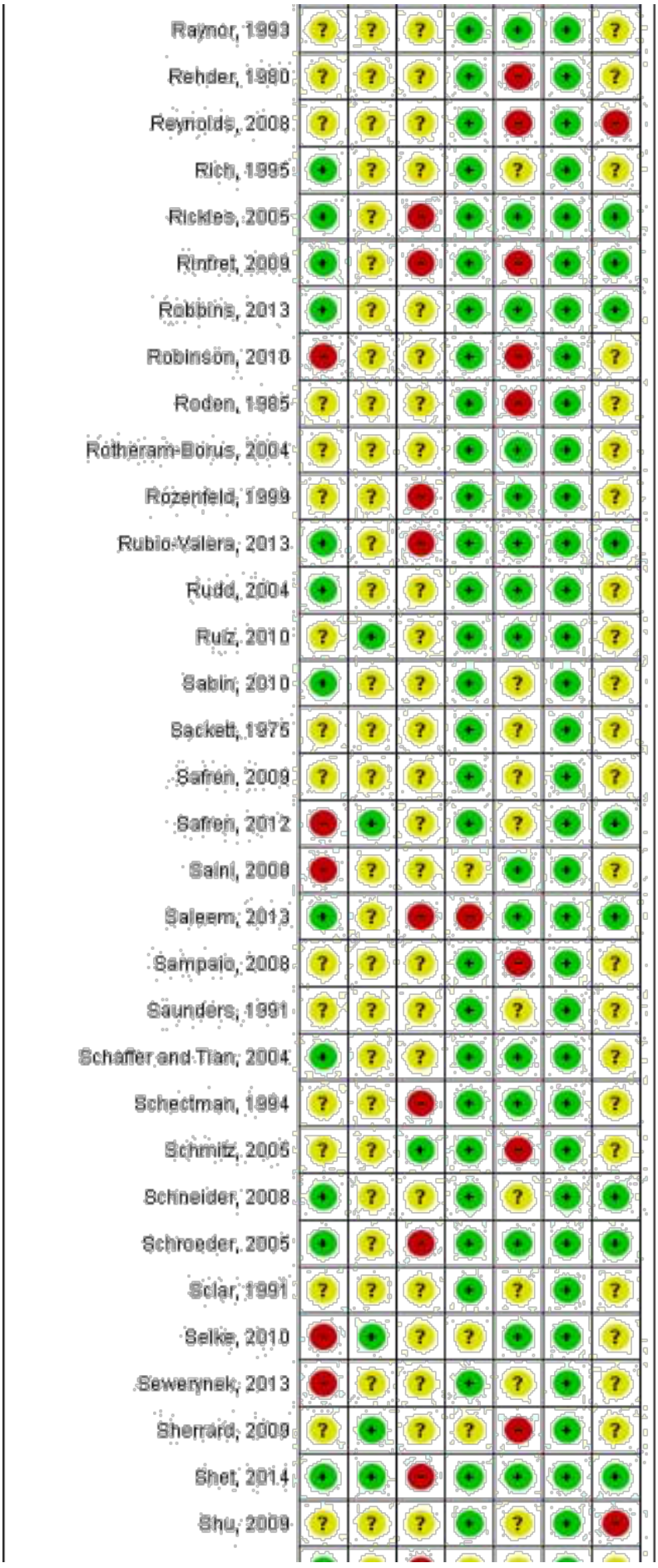
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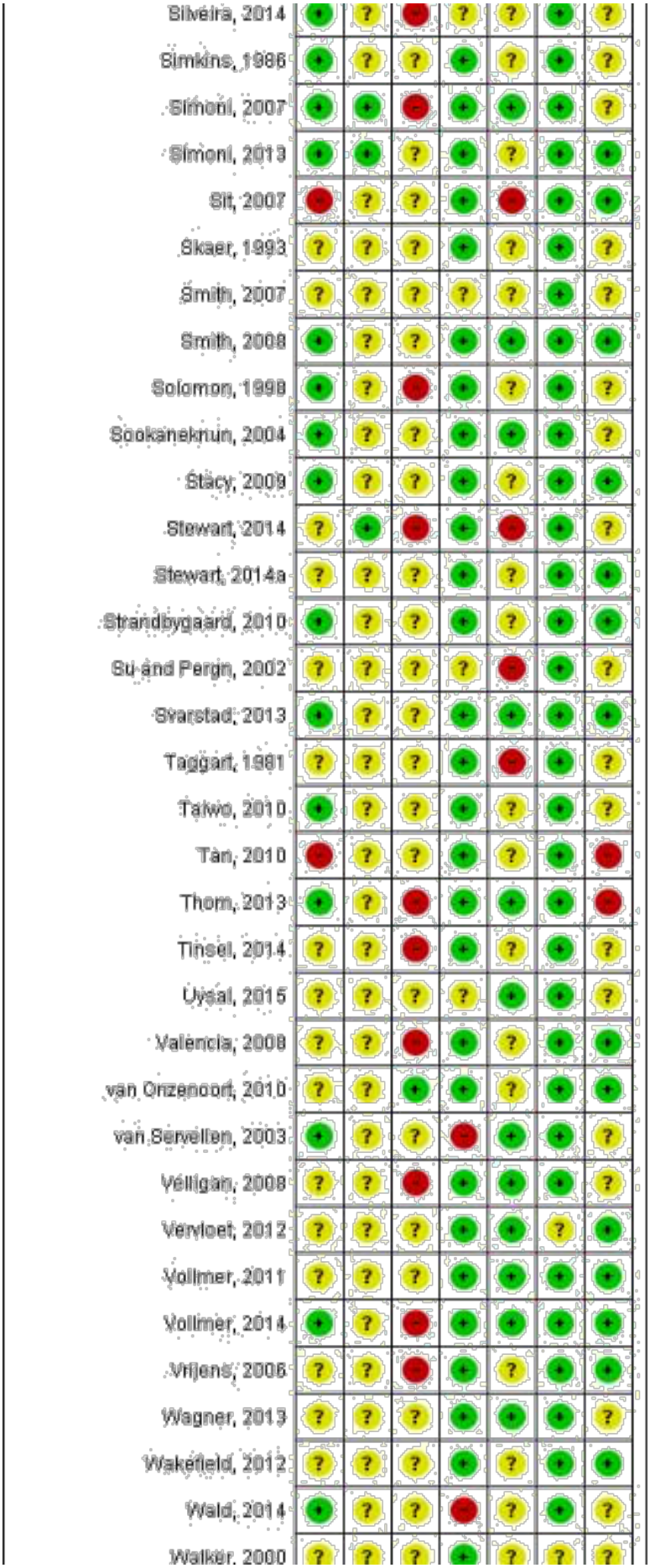
Shu, 2009


Silveira, 2014
Simkins, 1986
Simoni, 2007
Simoni, 2013
Sit, 2007
Skaer, 1993
Smith, 2007
Smith, 2008
Solomon, 1999
Sookanekrun, 2004
Stacy, 2009
Stewart, 2014
Stewart, 2014a
Strandbygaard, 2010
Su and Pergn, 2002
Svarstad, 2013
Taggart, 1981
Taiwo, 2010
Tan, 2010
Thom, 2013
Tinsel, 2014
Uysal, 2015
Valencia, 2008
van Onzenoort, 2010
van Servellen, 2003
Velligan, 2008
Vervloet, 2012
Vollmer, 2011
Vollmer, 2014
Vrijens, 2006
Wagner, 2013
Wakefield, 2012
Wald, 2014
Walker, 2000

S4 Table. Heterogenity between trials comparisons for the composite measure.

1st period – Composite measure		
Direct comparison	**Studies**	**I^2**
Attitudinal + Technical x Attitudinal	1	-
Attitudinal x Educational	3	0%
Attitudinal x Educational + Attitudinal + Technical	1	-
Attitudinal x Standard care	7	0%
Educational x Educational + Technical	2	33.0%
Educational x Educational + Attitudinal	2	11.2%
Educational x Technical	1	-
Educational x Standard care	30	54.5%
Educational + Attitudinal x Standard care	13	69.1%
Technical x Rewards + Technical	1	-
Technical x Attitudinal + Technical + Rewards	1	-
Technical x Standard care	31	37.1%
Rewards + Technical x Standard care	1	-
Rewards x Standard care	1	-
Educational + Attitudinal + Technical x Standard care	6	4.4%
Educational + Technical x Standard care	7	60.3%
2nd period – Composite measure		
Direct comparison	**Studies**	**I^2**
Attitudinal x Educational	4	74.5%
Attitudinal x Standard care	7	2.2%
Educational x Attitudinal + Rewards	1	-
Educational x Educational + Technical	6	45.3%
Educational x Technical	5	17.0%
Educational x Educational + Attitudinal	1	-
Educational x Standard care	31	67.1%
Educational + Technical x Standard care	16	54.2%
Educational + Technical x Technical	1	-
Educational + Attitudinal x Standard care	16	61.3%
Technical x Standard care	24	81.6%
Educational + Attitudinal + Technical x Standard care	7	39.0%
3rd period – Composite measure		
Direct comparison	**Studies**	**I^2**
Attitudinal x Educational + Attitudinal + Technical	1	-
Attitudinal x Standard care	3	42.8%
Educational + Attitudinal + Technical x Educational + Technical	1	-
Educational + Attitudinal + Technical x Educational + Attitudinal	1	-
Educational + Attitudinal + Technical x Standard care	3	13.0%
Educational + Technical x Standard care	5	64.5%
Educational + Technical x Educational + Attitudinal	1	-
Educational + Attitudinal x Educational	1	-
Educational + Attitudinal x Standard care	4	65.9%
Educational x Standard care	2	0%
Technical x Standard care	3	0%
4th period – Composite measure		
Direct comparison	**Studies**	**I^2**

Rewards x Standard care	1	-
Attitudinal + Technical x Technical	1	-
Attitudinal + Technical x Standard care	1	-
Educational + Attitudinal + Technical x Standard care	4	58.1%
Educational + Attitudinal + Rewards x Standard care	1	-
Attitudinal x Educational	4	10.3%
Attitudinal x Standard care	8	67.1%
Educational + Attitudinal x Educational	2	-
Educational + Attitudinal x Standard care	7	72.4%
Educational x Educational + Technical	1	-
Educational x Technical	2	0%
Educational x Standard care	20	89.7%
Educational + Technical x Technical	2	-
Educational + Technical x Standard care	26	87.9%
Technical x Standard care	22	91.8%
Rewards + Technical x Technical	1	-

S5 Table. Node-splitting analyses

0-3 months

Name	Direct Effect	Indirect Effect	Overall	P-Value
Attitudinal 1st , Educational 1st	-0,33 (-1,25, 0,56)	0,00 (-0,57, 0,58)	-0,09 (-0,57, 0,38)	0.53
Attitudinal 1st , Educational + Attitudinal + Technical 1st	-0,46 (-2,04, 1,10)	-0,32 (-1,07, 0,42)	-0,33 (-1,03, 0,36)	0.87
Attitudinal 1st , Standard care 1st	-0,53 (-1,03, -0,02)	-0,82 (-1,66, -0,02)	-0,61 (-1,05, -0,16)	0.53
Educational 1st, Educational + Attitudinal 1st	0,35 (-0,77, 1,51)	-0,03 (-0,48, 0,45)	0,03 (-0,39, 0,44)	0.55
Educational 1st, Educational + Technical 1st	0,96 (-0,03, 1,94)	0,00 (-0,64, 0,63)	0,29 (-0,24, 0,84)	0.1
Educational 1st, Standard care 1st	-0,58 (-0,87, -0,29)	0,04 (-0,59, 0,66)	-0,48 (-0,75, -0,20)	0.06
Educational 1st, Technical 1st	0,96 (-0,49, 2,48)	0,05 (-0,33, 0,42)	0,08 (-0,28, 0,44)	0.23
Educational + Attitudinal 1st, Standard care 1st	-0,50 (-0,89, -0,13)	-0,88 (-2,08, 0,32)	-0,54 (-0,91, -0,19)	0.56
Educational + Technical 1st, Standard care 1st	-0,66 (-1,23, -0,13)	-1,37 (-2,35, -0,39)	-0,81 (-1,32, -0,32)	0.21

4-6 months

Name	Direct Effect	Indirect Effect	Overall	P-Value
Attitudinal 2nd, Educational 2nd	-0,63 (-1,47, 0,20)	-0,14 (-0,82, 0,53)	-0,33 (-0,86, 0,19)	0.37
Attitudinal 2nd, Standard care 2nd	-0,60 (-1,23, 0,02)	-1,11 (-1,97, -0,26)	-0,77 (-1,28, -0,27)	0.35
Educational 2nd, Educational + Attitudinal 2nd	0,87 (-0,99, 2,94)	0,06 (-0,39, 0,51)	0,09 (-0,34, 0,53)	0.59
Educational 2nd, Educational + Technical 2nd	0,61 (0,01, 1,24)	-0,10 (-0,59, 0,39)	0,18 (-0,20, 0,56)	0.07
Educational 2nd, Standard care 2nd	-0,54 (-0,81, -0,28)	0,00 (-0,47, 0,49)	-0,43 (-0,68, -0,18)	0.06
Educational 2nd, Technical 2nd	0,88 (0,20, 1,57)	0,59 (0,18, 1,00)	0,65 (0,28, 1,01)	0.45
Educational + Attitudinal 2nd, Standard care 2nd	-0,47 (-0,86, -0,09)	-1,26 (-3,33, 0,61)	-0,50 (-0,87, -0,11)	0.5
Educational + Technical 2nd, Standard care 2nd	-0,54 (-0,94, -0,15)	-0,92 (-1,55, -0,28)	-0,61 (-0,96, -0,27)	0.3
Educational + Technical 2nd, Technical 2nd	0,48 (-0,71, 1,73)	0,44 (-0,03, 0,90)	0,47 (0,03, 0,90)	0.94

7-9 months

Name	Direct Effect	Indirect Effect	Overall	P-Value
Attitudinal 3rd, Educational + Attitudinal + Technical 3rd	-0,17 (-1,68, 1,31)	-0,47 (-1,72, 0,69)	-0,31 (-1,31, 0,67)	0.73
Educational 3rd, Educational + Attitudinal 3rd	1,02 (-0,39, 2,45)	0,17 (-0,83, 1,07)	0,35 (-0,36, 1,24)	0.26
Educational 3rd, Standard care 3rd	-0,14 (-0,89, 0,62)	0,75 (-0,75, 2,26)	-0,03 (-0,62, 0,70)	0.25
Educational + Attitudinal 3rd, Educational + Attitudinal + Technical 3rd	0,17 (-1,04, 1,51)	0,48 (-0,68, 1,73)	0,23 (-0,59, 1,11)	0.68
Educational + Attitudinal 3rd, Educational + Technical 3rd	0,56 (-0,70, 1,87)	0,34 (-0,54, 1,37)	0,41 (-0,34, 1,20)	0.74
Educational + Attitudinal 3rd, Standard care 3rd	-0,27 (-0,88, 0,38)	-0,70 (-1,73, 0,29)	-0,37 (-0,96, 0,14)	0.42
Educational + Attitudinal + Technical 3rd, Educational + Technical 3rd	0,30 (-0,99, 1,68)	0,10 (-1,02, 1,25)	0,20 (-0,72, 1,06)	0.78

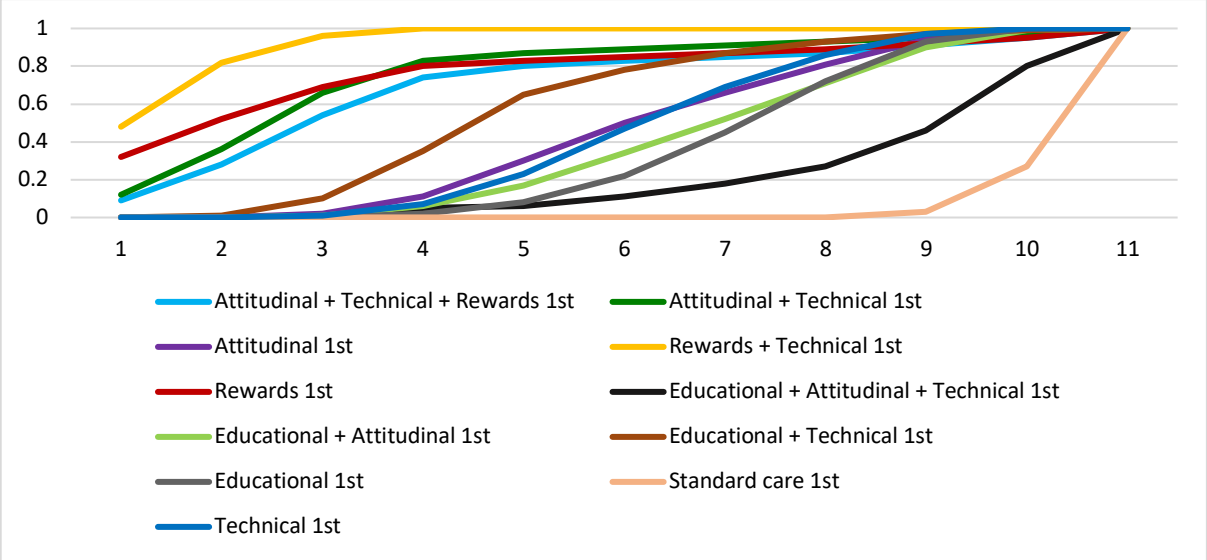
≥10 months

Name	Direct Effect	Indirect Effect	Overall	P-Value
Attitudinal 4th, Educational 4th	-0,29 (-0,86, 0,28)	0,34 (-0,20, 0,87)	0,04 (-0,36, 0,43)	0.12
Attitudinal 4th, Standard care 4th	-0,26 (-0,75, 0,19)	-0,89 (-1,52, -0,26)	-0,50 (-0,88, -0,12)	0.12
Educational 4th, Educational + Attitudinal 4th	0,28 (-0,74, 1,28)	-0,32 (-0,91, 0,25)	-0,18 (-0,67, 0,33)	0.32
Educational 4th, Educational + Technical 4th	-0,43 (-1,44, 0,57)	0,09 (-0,27, 0,45)	0,03 (-0,30, 0,39)	0.33
Educational 4th, Standard care 4th	-0,62 (-0,90, -0,33)	-0,26 (-0,79, 0,28)	-0,53 (-0,79, -0,27)	0.23
Educational + Attitudinal 4th, Standard care 4th	-0,24 (-0,76, 0,27)	-0,86 (-1,91, 0,18)	-0,36 (-0,82, 0,10)	0.28
Educational + Technical 4th, Standard care 4th	-0,60 (-0,86, -0,36)	-0,19 (-0,88, 0,51)	-0,57 (-0,82, -0,33)	0.27
Educational + Technical 4th, Technical 4th	0,21 (-0,70, 1,12)	-0,07 (-0,46, 0,31)	-0,06 (-0,42, 0,30)	0.56

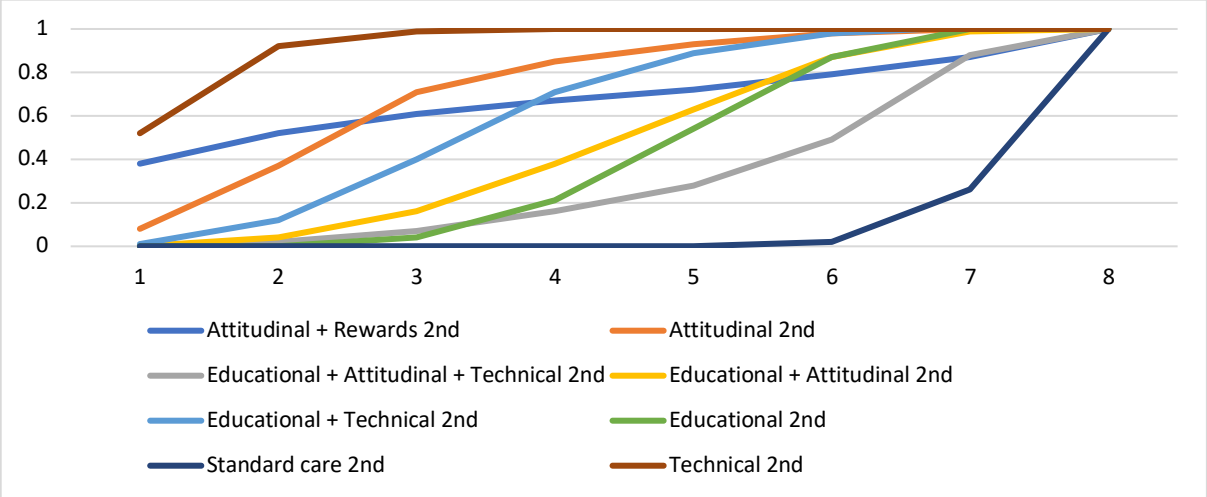
S2 Figure. SUCRA analyses

Surface Under the Cumulative Ranking curve (SUCRA) for composite measures for each time period (0-3 months, 4-6 months, 7-9 months, >10 months). SUCRA values can range from 0% (i.e. the treatment always ranks last) to 100% (i.e. the treatment always ranks first).

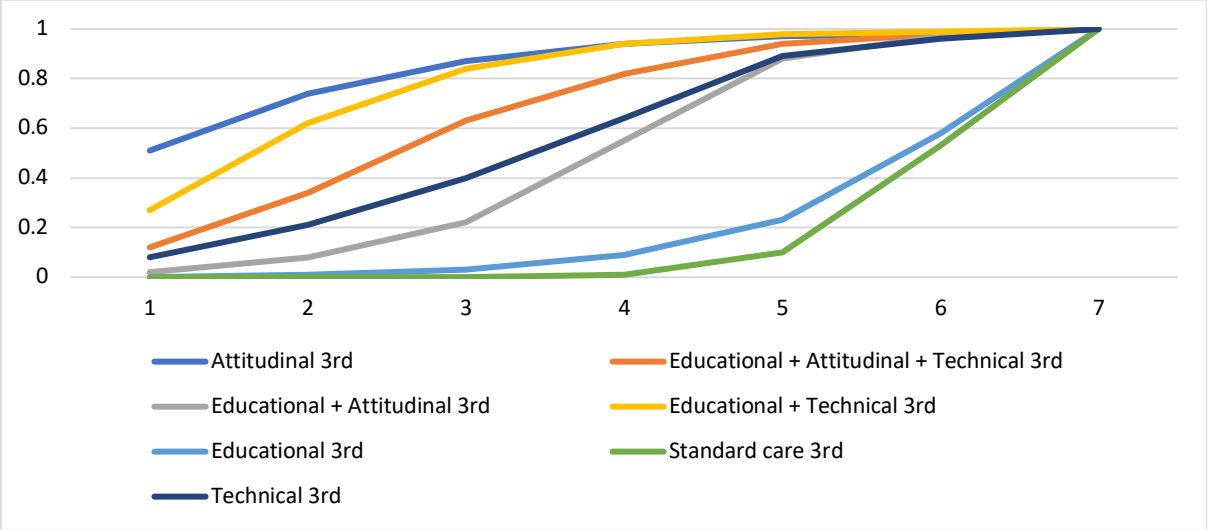
0-3 months



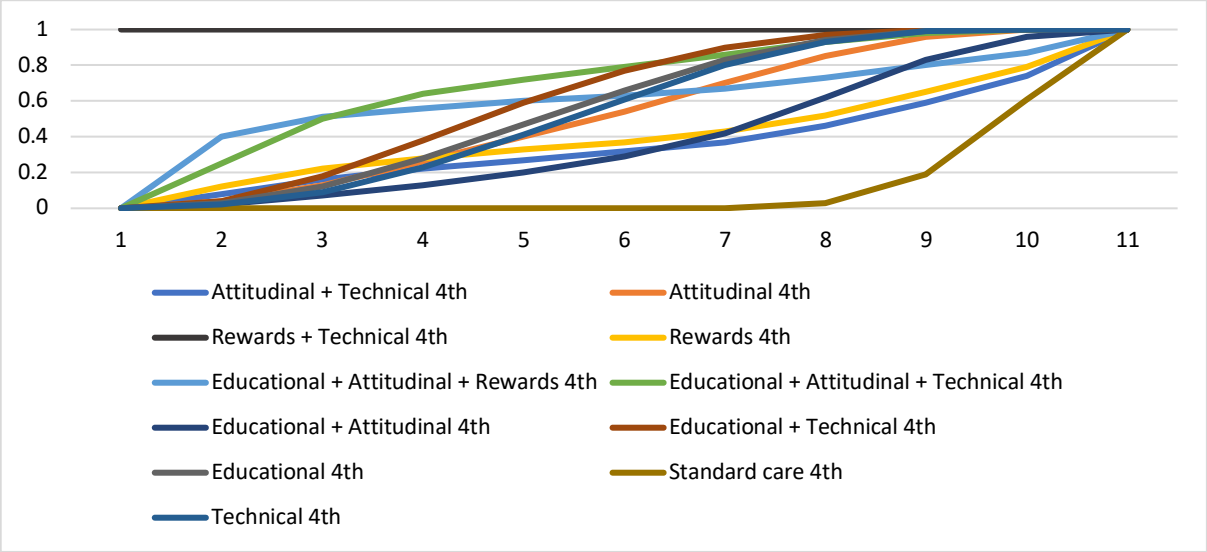
4-6 months



7-9 months


1
0.8
0.6
0.4
0.2
0
1
2
3
4
5
6
7
Attitudinal 3rd
Educational + Attitudinal + Technical 3rd
Educational + Attitudinal 3rd
Educational + Technical 3rd
Educational 3rd
Standard care 3rd
Technical 3rd

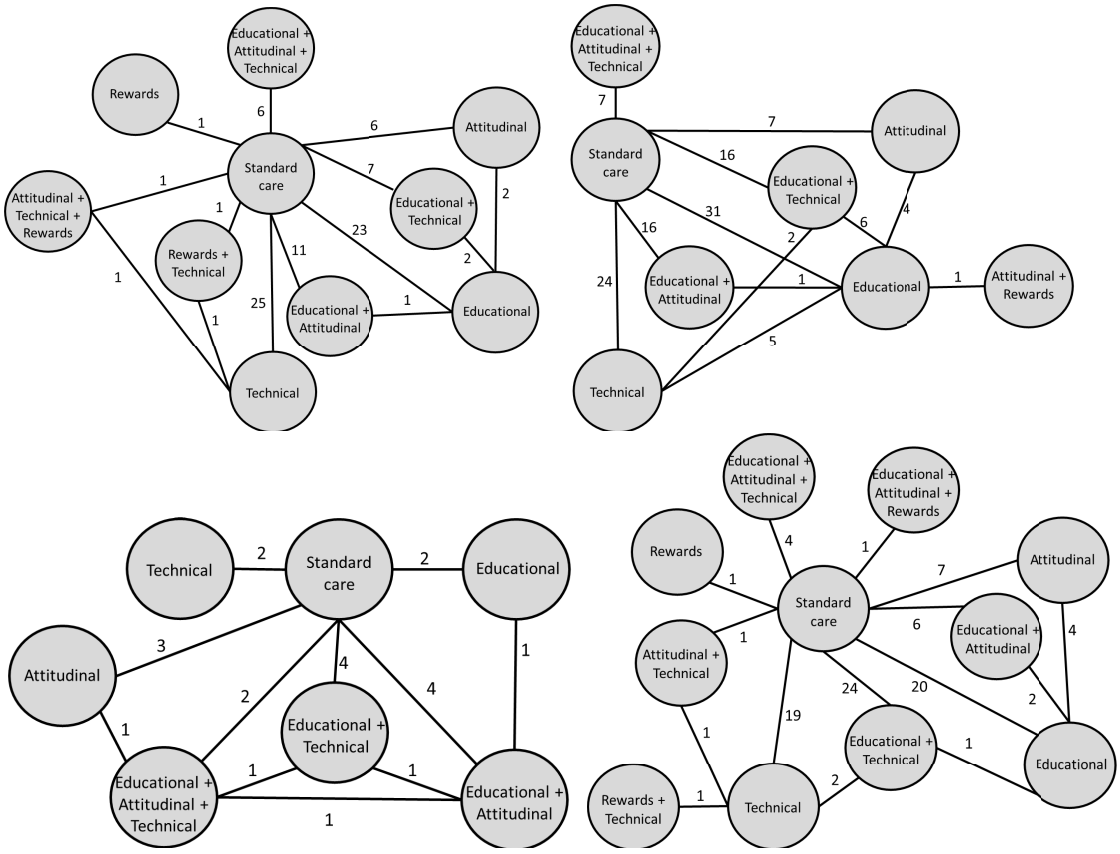
≥10 months


1
0.8
0.6
0.4
0.2
0
1
2
3
4
5
6
7
8
9
10
11
Attitudinal + Technical 4th
Attitudinal 4th
Rewards + Technical 4th
Rewards 4th
Educational + Attitudinal + Rewards 4th
Educational + Attitudinal + Technical 4th
Educational + Attitudinal 4th
Educational + Technical 4th
Educational 4th
Standard care 4th
Technical 4th

S1 File. Sensitivity and sub-group analyses

Figure A and Tables A-D. Sample size >30

Fig A. Networks of the comparisons between interventions with sample size >30 for each time period (0-3 months, 4-6 months, 7-9 months, ≥10 months) (top left to bottom right) considering the overall composite measure of adherence. Each node represents an intervention. Directly comparable interventions are linked with a line, the number of trials for each comparison are shown in each line.



Tables A-D. Consistency analyses of multiple comparison analyses for the overall composite measure in studies with sample size >30 in 0-3 months, 4-6 months, 7-9 months, and ≥10 months.
Effect sizes are reported as OR (with 95% CrI). Comparisons are read from left to right (row to column above, column to row below). An OR <1 indicates a more effective intervention. Bold data comparisons are statistically significant. Edu: educational, Att: attitudinal, Tec: technical, Rew: rewards, SOC: standard of care.

Table A. 0-3 months

Att + Tec + Rew 1st	0,44 (0,06, 2,49)	2,83 (0,32, 22,78)	1,72 (0,07, 95,26)	0,33 (0,05, 1,93)	0,40 (0,06, 2,18)	0,55 (0,08, 3,15)	0,39 (0,06, 2,12)	0,25 (0,04, 1,33)	0,45 (0,07, 2,38)
	Att 1st	***6,56 (1,60, 26,28)***	3,85 (0,31, 177,10	0,75 (0,38, 1,46)	0,90 (0,52, 1,59)	1,26 (0,65, 2,39)	0,88 (0,54, 1,42)	***0,57 (0,36, 0,88)***	1,01 (0,60, 1,68)
		Rew + Tec 1st	0,61 (0,04, 29,08)	***0,12 (0,03, 0,46)***	***0,14 (0,04, 0,54)***	***0,19 (0,05, 0,79)***	***0,14 (0,03, 0,52)***	***0,09 (0,02, 0,32)***	***0,16 (0,04, 0,57)***
			Rew 1st	0,20 (0,00, 2,33)	0,24 (0,01, 2,74)	0,33 (0,01, 4,12)	0,23 (0,01, 2,69)	0,15 (0,00, 1,69)	0,26 (0,01, 3,05)
				Edu + Att + Tec 1st	1,21 (0,63, 2,35)	1,69 (0,83, 3,49)	1,18 (0,67, 2,14)	0,76 (0,45, 1,29)	1,35 (0,76, 2,46)
					Edu + Att 1st	1,40 (0,75, 2,55)	0,98 (0,63, 1,51)	***0,63 (0,43, 0,90)***	1,12 (0,71, 1,77)
						Edu + Tec 1st	0,70 (0,42, 1,17)	***0,45 (0,28, 0,73)***	0,80 (0,46, 1,40)
							Edu 1st	***0,64 (0,49, 0,83)***	1,14 (0,79, 1,66)
								SOC 1st	***1,78 (1,36, 2,35)***
									Tec 1st

Table B. 4-6 months

Att + Rew 2nd	0,65 (0,12, 3,64)	0,49 (0,09, 2,73)	0,73 (0,14, 3,89)	0,73 (0,15, 3,76)	0,67 (0,14, 3,25)	0,41 (0,08, 2,02)	1,24 (0,25, 6,31)
	Att 2nd	0,75 (0,32, 1,76)	1,13 (0,54, 2,41)	1,10 (0,54, 2,34)	1,02 (0,53, 1,97)	0,62 (0,33, 1,18)	1,91 (0,93, 3,85)
		Edu + Att + Tec 2	1,50 (0,77, 2,94)	1,47 (0,76, 2,90)	1,37 (0,73, 2,52)	0,83 (0,47, 1,44)	***2,52 (1,34, 4,73)***
			Edu + Att 2nd	0,99 (0,59, 1,65)	0,91 (0,57, 1,44)	***0,55 (0,38, 0,81)***	***1,69 (1,04, 2,76)***
				Edu + Tec 2nd	0,92 (0,62, 1,37)	***0,56 (0,39, 0,79)***	***1,71 (1,10, 2,68)***
					Edu 2nd	***0,61 (0,47, 0,78)***	***1,86 (1,27, 2,71)***
						SOC 2nd	***3,05 (2,25, 4,17)***
							Tec 2nd

Table C. 7-9 months

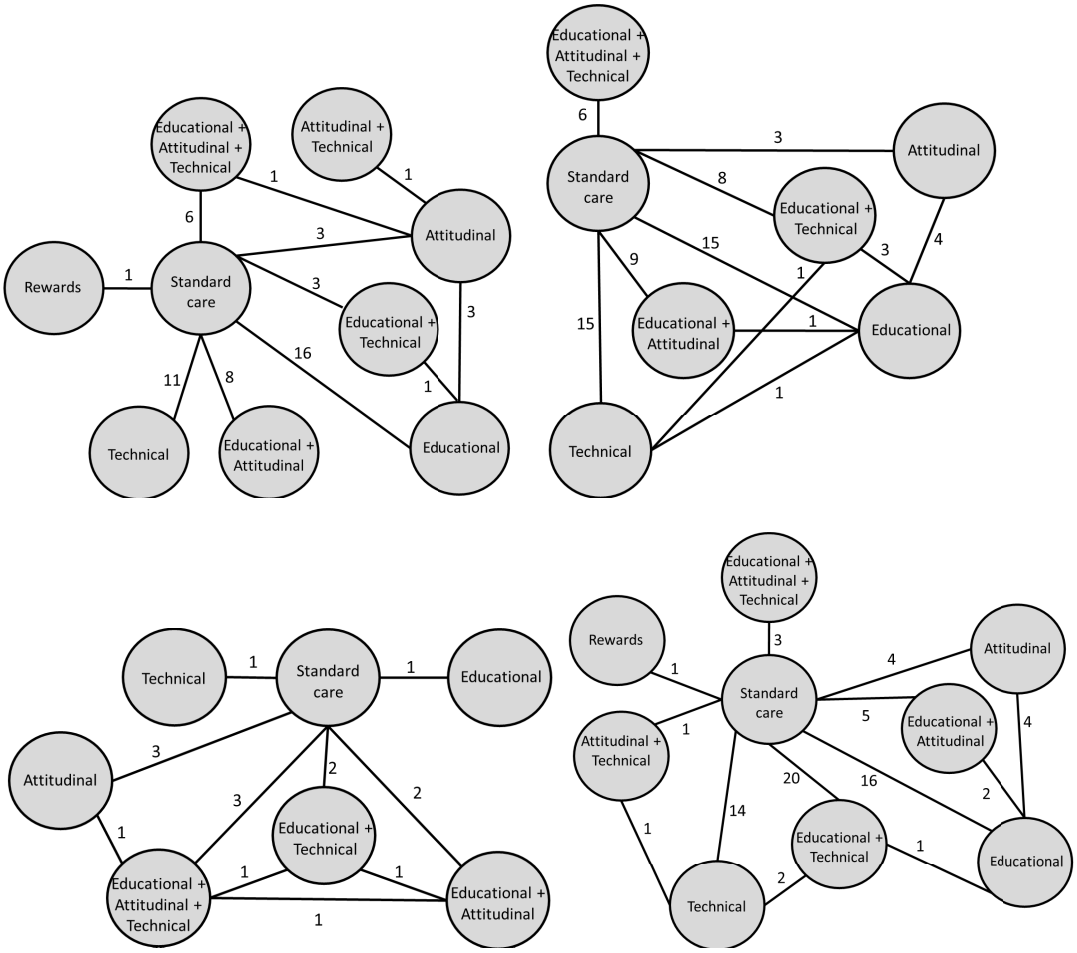
Att 3rd	0,72 (0,23, 2,21)	0,56 (0,20, 1,50)	0,82 (0,27, 2,41)	***0,45 (0,12, 0,98)***	***0,38 (0,16, 0,84)***	0,55 (0,16, 1,79)
	Edu + Att + Tec 3rd	0,79 (0,28, 2,15)	1,14 (0,39, 3,31)	0,53 (0,15, 1,58)	0,53 (0,20, 1,31)	0,77 (0,20, 2,65)
		Edu + Att 3rd	1,45 (0,63, 3,54)	0,67 (0,27, 1,49)	0,67 (0,36, 1,21)	0,98 (0,32, 2,85)
			Edu + Tec 3rd	0,46 (0,16, 1,19)	***0,46 (0,22, 0,92)***	0,67 (0,21, 2,07)
				Edu 3rd	1,00 (0,49, 2,25)	1,44 (0,47, 4,77)
					SOC 3rd	1,46 (0,59, 3,51)
						Tec 3rd

Table D. ≥10 months

Att + Tec 4th	1,36 (0,47, 3,94)	***24,14 (4,68, 140,***	1,08 (0,26, 4,55)	1,63 (0,31, 8,68)	1,60 (0,50, 5,01)	1,26 (0,42, 3,75)	1,30 (0,47, 3,65)	1,37 (0,49, 3,82)	0,78 (0,29, 2,14)	1,31 (0,49, 3,53)
	Att 4th	***17,97 (4,31, 78,5***	0,80 (0,27, 2,37)	1,20 (0,30, 4,79)	1,18 (0,58, 2,38)	0,92 (0,51, 1,70)	0,96 (0,61, 1,52)	1,00 (0,67, 1,50)	***0,58 (0,39, 0,85)***	0,96 (0,61, 1,54)
		Rew + Tec 4th	***0,04 (0,01, 0,25)***	***0,07 (0,01, 0,45)***	***0,07 (0,01, 0,29)***	***0,05 (0,01, 0,22)***	***0,05 (0,01, 0,21)***	***0,06 (0,01, 0,23)***	***0,03 (0,01, 0,12)***	***0,05 (0,01, 0,20)***
			Rew 4th	1,49 (0,28, 8,08)	1,47 (0,45, 4,64)	1,16 (0,38, 3,48)	1,21 (0,41, 3,42)	1,26 (0,44, 3,60)	0,73 (0,26, 1,98)	1,22 (0,42, 3,43)
				Edu + Att + Rew 4t	0,97 (0,23, 4,08)	0,77 (0,19, 3,17)	0,80 (0,21, 3,06)	0,84 (0,21, 3,21)	0,48 (0,13, 1,81)	0,79 (0,21, 3,08)
					Edu + Att + Tec 4	0,79 (0,38, 1,62)	0,82 (0,44, 1,50)	0,85 (0,45, 1,58)	***0,49 (0,28, 0,87)***	0,82 (0,43, 1,55)
						Edu + Att 4th	1,04 (0,63, 1,75)	1,08 (0,65, 1,78)	***0,63 (0,39, 0,99)***	1,05 (0,61, 1,76)
							Edu + Tec 4th	1,04 (0,74, 1,46)	***0,60 (0,47, 0,76)***	1,00 (0,71, 1,40)
								Edu 4th	***0,58 (0,45, 0,74)***	0,96 (0,68, 1,39)
									SOC 4th	***1,67 (1,30, 2,15)***
										Tec 4th

Figure B and Tables E-H. After 2007

Fig B. Networks of the comparisons between interventions in studies published after 2007 for each time period (0-3 months, 4-6 months, 7-9 months, ≥10 months) (top left to bottom right) considering the overall composite measure of adherence. Each node represents an intervention. Directly comparable interventions are linked with a line, the number of trials for each comparison are shown in each line.



Tables E-H. Consistency analyses of multiple comparison analyses for the overall composite measure in studies published after 2007 in 0-3 months, 4-6 months, 7-9 months, and ≥10 months.
Effect sizes are reported as OR (with 95% CrI). Comparisons are read from left to right (row to column above, column to row below). An OR <1 indicates a more effective intervention. Bold data comparisons are statistically significant. Edu: educational, Att: attitudinal, Tec: technical, Rew: rewards, SOC: standard of care.

Table E. 0-3 months

Att + Tec 1st	0,37 (0,08, 1,63)	1,14 (0,07, 50,98)	0,23 (0,04, 1,20)	0,32 (0,06, 1,66)	0,32 (0,05, 1,88)	0,32 (0,06, 1,56)	***0,17 (0,03, 0,85)***	0,32 (0,06, 1,64)
	Att 1st	3,06 (0,27, 111,7	0,62 (0,29, 1,33)	0,87 (0,42, 1,80)	0,85 (0,34, 2,21)	0,86 (0,48, 1,55)	***0,47 (0,27, 0,82)***	0,85 (0,41, 1,79)
		Rew 1st	0,21 (0,01, 2,26)	0,28 (0,01, 3,10)	0,28 (0,01, 3,28)	0,28 (0,01, 3,07)	0,15 (0,00, 1,59)	0,28 (0,01, 3,01)
			Edu + Att + Tec 1s	1,39 (0,68, 2,86)	1,37 (0,55, 3,54)	1,39 (0,74, 2,56)	0,75 (0,44, 1,29)	1,36 (0,67, 2,81)
				Edu + Att 1st	0,97 (0,41, 2,45)	0,99 (0,56, 1,73)	***0,54 (0,33, 0,85)***	0,98 (0,51, 1,90)
					Edu + Tec 1st	1,02 (0,44, 2,23)	0,56 (0,25, 1,09)	1,00 (0,41, 2,41)
						Edu 1st	***0,54 (0,39, 0,76)***	0,98 (0,57, 1,75)
							SOC 1st	***1,80 (1,15, 2,91)***
								Tec 1st

Table F. 4-6 months

Att 2nd	0,53 (0,22, 1,27)	0,63 (0,28, 1,40)	0,63 (0,28, 1,38)	0,74 (0,38, 1,40)	***0,39 (0,20, 0,77)***	1,03 (0,47, 2,21)
	Edu + Att + Tec 2n	1,19 (0,59, 2,47)	1,18 (0,59, 2,39)	1,40 (0,74, 2,60)	0,73 (0,43, 1,26)	***1,95 (1,03, 3,75)***
		Edu + Att 2nd	0,99 (0,54, 1,88)	1,17 (0,67, 2,05)	***0,61 (0,39, 0,99)***	1,64 (0,91, 2,97)
			Edu + Tec 2nd	1,19 (0,71, 1,91)	***0,62 (0,40, 0,94)***	***1,66 (1,02, 2,84)***
				Edu 2nd	***0,52 (0,38, 0,73)***	1,40 (0,86, 2,25)
					SOC 2nd	***2,66 (1,86, 3,76)***
						Tec 2nd

Table G. 7-9 months

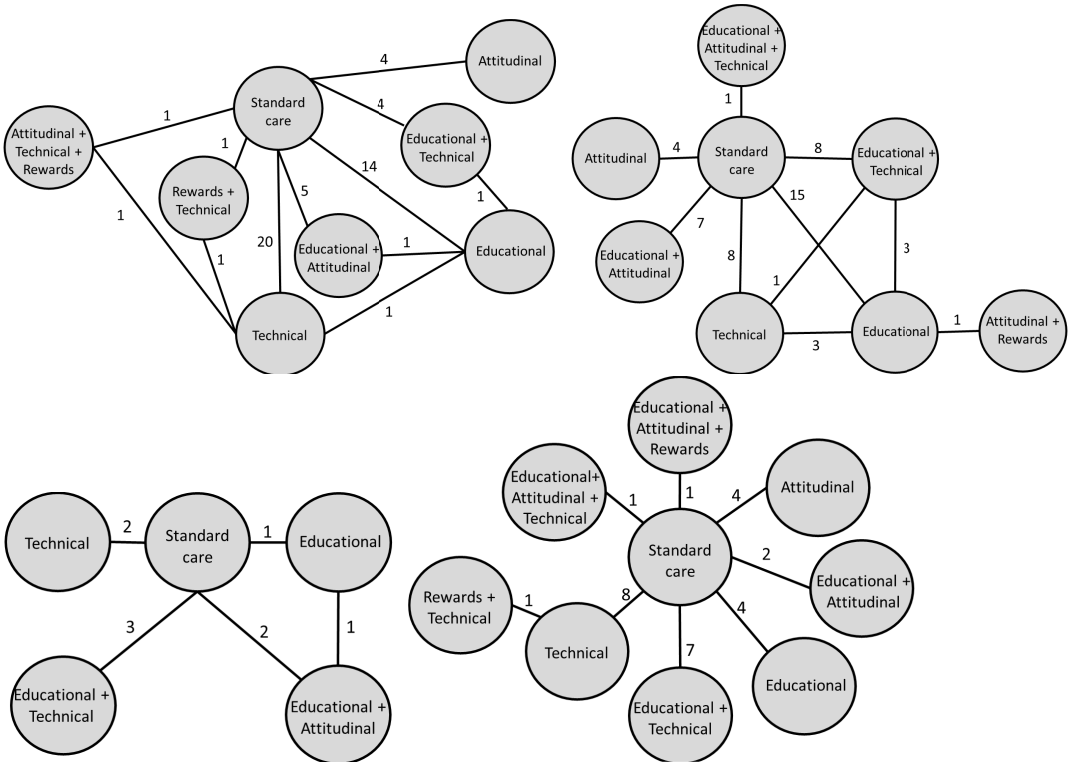
Att 3rd	0,68 (0,24, 1,90)	0,36 (0,11, 1,14)	0,94 (0,28, 3,13)	0,49 (0,12, 1,93)	***0,39 (0,16, 0,85)***	0,59 (0,13, 2,29)
	Edu + Att + Tec 3rd	0,53 (0,19, 1,52)	1,38 (0,47, 4,18)	0,72 (0,17, 2,87)	0,58 (0,25, 1,26)	0,87 (0,20, 3,42)
		Edu + Att 3rd	2,57 (0,89, 7,92)	1,36 (0,31, 5,98)	1,08 (0,44, 2,55)	1,62 (0,35, 6,59)
			Edu + Tec 3rd	0,52 (0,11, 2,23)	0,42 (0,16, 1,02)	0,63 (0,13, 2,60)
				Edu 3rd	0,81 (0,24, 2,56)	1,21 (0,23, 5,84)
					SOC 3rd	1,49 (0,46, 4,94)
						Tec 3rd

Table H. ≥10 months

Att + Tec 4th	1,41 (0,44, 4,36)	1,08 (0,25, 4,97)	1,79 (0,53, 5,92)	0,99 (0,30, 3,13)	1,32 (0,45, 3,74)	1,29 (0,44, 3,64)	0,78 (0,27, 2,15)	1,32 (0,47, 3,67)
	Att 4th	0,77 (0,23, 2,53)	1,28 (0,57, 2,93)	0,70 (0,35, 1,41)	0,94 (0,55, 1,61)	0,91 (0,58, 1,42)	***0,56 (0,35, 0,89)***	0,94 (0,54, 1,67)
		Rew 4th	1,65 (0,47, 5,89)	0,91 (0,27, 3,05)	1,21 (0,41, 3,68)	1,18 (0,39, 3,68)	0,72 (0,24, 2,14)	1,23 (0,40, 3,79)
			Edu + Att + Tec 4t	0,55 (0,24, 1,27)	0,73 (0,36, 1,48)	0,71 (0,35, 1,45)	***0,44 (0,22, 0,83)***	0,74 (0,36, 1,52)
				Edu + Att 4th	1,33 (0,73, 2,43)	1,29 (0,73, 2,31)	0,79 (0,46, 1,37)	1,34 (0,72, 2,54)
					Edu + Tec 4th	0,98 (0,67, 1,43)	***0,60 (0,45, 0,78)***	1,01 (0,68, 1,50)
						Edu 4th	***0,61 (0,46, 0,81)***	1,03 (0,68, 1,60)
							SOC 4th	***1,70 (1,25, 2,33)***
								Tec 4th

Figure C and Tables I-L. Before 2007

Fig C. Networks of the comparisons between interventions in studies published before 2007 for each time period (0-3 months, 4-6 months, 7-9 months, ≥10 months) (top left to bottom right) considering the overall composite measure of adherence. Each node represents an intervention. Directly comparable interventions are linked with a line, the number of trials for each comparison are shown in each line.



Tables I-L. Consistency analyses of multiple comparison analyses for the overall composite measure in studies published before 2007 in 0-3 months, 4-6 months, 7-9 months, and ≥10 months.

Effect sizes are reported as OR (with 95% CrI). Comparisons are read from left to right (row to column above, column to row below). An OR <1 indicates a more effective intervention. Bold data comparisons are statistically significant. Edu: educational, Att: attitudinal, Tec: technical, Rew: rewards, SOC: standard of care.

Table I. 0-3 months

Att + Tec + Rew 1s	0,38 (0,05, 2,67)	2,81 (0,25, 30,54)	0,40 (0,05, 2,49)	0,61 (0,07, 4,19)	0,38 (0,05, 2,38)	0,25 (0,03, 1,49)	0,45 (0,06, 2,70)
	Att 1st	***7,36 (1,42, 40,98***	1,00 (0,38, 2,79)	1,58 (0,54, 4,63)	0,98 (0,41, 2,37)	0,64 (0,30, 1,41)	1,15 (0,50, 2,74)
		Rew + Tec 1st	***0,14 (0,03, 0,68)***	0,22 (0,04, 1,11)	***0,13 (0,03, 0,61)***	***0,09 (0,02, 0,38)***	***0,16 (0,03, 0,67)***
			Edu + Att 1st	1,59 (0,59, 3,99)	0,97 (0,47, 1,94)	0,64 (0,34, 1,17)	1,14 (0,54, 2,31)
				Edu + Tec 1st	0,62 (0,28, 1,39)	***0,40 (0,19, 0,85)***	0,72 (0,32, 1,66)
					Edu 1st	***0,66 (0,43, 0,98)***	1,18 (0,68, 2,02)
						SOC 1st	***1,79 (1,24, 2,60)***
							Tec 1st

Table J. 4-6 months

Att + Rew 2nd	1,14 (0,14, 8,72)	0,58 (0,05, 6,88)	0,95 (0,14, 6,33)	1,23 (0,18, 8,27)	0,68 (0,11, 3,96)	0,54 (0,09, 3,38)	1,67 (0,24, 11,42
	Att 2nd	0,51 (0,08, 3,36)	0,84 (0,28, 2,47)	1,09 (0,37, 3,24)	0,60 (0,22, 1,58)	0,48 (0,20, 1,17)	1,46 (0,50, 4,40)
		Edu + Att + Tec 2	1,65 (0,29, 9,29)	2,16 (0,38, 12,60)	1,19 (0,22, 6,22)	0,96 (0,19, 4,74)	2,93 (0,51, 16,58
			Edu + Att 2nd	1,30 (0,55, 3,10)	0,71 (0,33, 1,49)	0,57 (0,31, 1,05)	1,75 (0,73, 4,14)
				Edu + Tec 2nd	0,55 (0,27, 1,10)	***0,44 (0,23, 0,81)***	1,35 (0,58, 3,09)
					Edu 2nd	0,80 (0,52, 1,24)	***2,45 (1,23, 4,94)***
						SOC 2nd	***3,06 (1,68, 5,62)***
							Tec 2nd

Table K. 7-9 months

Edu + Att 3rd	0,85 (0,15, 6,06)	0,44 (0,09, 2,05)	0,46 (0,13, 1,66)	0,91 (0,14, 9,05)
	Edu + Tec 3rd	0,52 (0,06, 3,20)	0,53 (0,14, 1,75)	1,08 (0,15, 9,12)
		Edu 3rd	1,03 (0,23, 4,84)	2,06 (0,28, 23,29)
			SOC 3rd	2,01 (0,47, 12,23)
				Tec 3rd

Table L. ≥10 months

Att 4th	***23,38 (3,97, 149,7***	1,70 (0,30, 9,61)	0,92 (0,17, 4,99)	1,59 (0,45, 5,99)	1,85 (0,71, 5,00)	1,84 (0,61, 5,30)	0,81 (0,38, 1,74)	1,31 (0,53, 3,26)
	Rew + Tec 4th	***0,07 (0,01, 0,67)***	***0,04 (0,00, 0,36)***	***0,07 (0,01, 0,46)***	***0,08 (0,01, 0,43)***	***0,08 (0,01, 0,44)***	***0,03 (0,01, 0,17)***	***0,06 (0,01, 0,26)***
		Edu + Att + Rew	0,54 (0,06, 4,59)	0,94 (0,15, 6,05)	1,09 (0,21, 5,67)	1,09 (0,18, 6,08)	0,48 (0,10, 2,21)	0,77 (0,15, 3,99)
			Edu + Att + Tec 4t	1,75 (0,28, 11,10)	2,01 (0,40, 10,68	2,00 (0,36, 10,88	0,89 (0,19, 4,13)	1,43 (0,29, 7,31)
				Edu + Att 4th	1,16 (0,35, 3,80)	1,14 (0,31, 4,03)	0,51 (0,18, 1,40)	0,83 (0,26, 2,56)
					Edu + Tec 4th	0,99 (0,37, 2,44)	***0,44 (0,24, 0,77)***	0,70 (0,33, 1,49)
						Edu 4th	***0,44 (0,21, 0,95)***	0,72 (0,29, 1,80)
							SOC 4th	***1,63 (1,01, 2,66)***
								Tec 4th

S6 Table. Final rank orders from SUCRA analyses

Rank	0-3 months	4-6 months	7-9 months	≥10 months
1st	Rewards + Technical	Technical	Attitudinal	Rewards + Technical
2nd	Rewards	Attitudinal	Educational + Technical	Educational + Attitudinal + Technical
3rd	Attitudinal + Technical	Attitudinal + Rewards	Educational + Attitudinal + Technical	Educational + Attitudinal + Rewards
4th	Attitudinal + Technical + Rewards	Educational + Technical	Technical	Educational + Technical
5th	Educational + Technical	Educational + Attitudinal	Educational + Attitudinal	Educational
6th	Attitudinal	Educational	Educational	Technical
7th	Educational + Attitudinal	Educational + Attitudinal + Technical	Standard care	Attitudinal
8th	Technical	Standard care		Rewards
9th	Educational			Educational + Attitudinal
10th	Educational + Attitudinal + Technical			Attitudinal + Technical
11th	Standard care			Standard care

S2 File. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be	6 and

		repeated.	Supporting
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-12 and Supporting

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9 and Supporting
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-11 and Supporting
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9 and Supporting
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	In Submission

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	***1***
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	***4-5***
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	***6***
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one	6 and

		database, including any limits used, such that it could be repeated.	Supporting
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	*7*
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	8
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	8
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**7**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	***8***

RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	***Fig 2***
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	***9-10***
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-12 and Supporting
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	9 and Supporting
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	***10-14***
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	***10-11 and Supporting***
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	***10***
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	9 and Supporting
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	***14 and Supporting***
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	14-16

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	***In Submission***

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Box. Terminology: Reviews With Networks of Multiple Treatments

Different terms have been used to identify systematic reviews that incorporate a network of multiple treatment comparisons. A brief overview of common terms follows.

Indirect treatment comparison: Comparison of 2 interventions for which studies against a common comparator, such as placebo or a standard treatment, are available (i.e., indirect information). The direct treatment effects of each intervention against the common comparator (i.e., treatment effects from a comparison of interventions made within a study) may be used to estimate an indirect treatment comparison between the 2 interventions (**Appendix Figure 1, A**). An indirect treatment comparison (ITC) may also involve multiple links. For example, in **Appendix Figure 1, B**, treatments B and D may be compared indirectly on the basis of studies encompassing comparisons of B versus C, A versus C, and A versus D.

Network meta-analysis or *mixed treatment comparison*: These terms, which are often used interchangeably, refer to situations involving the simultaneous comparison of 3 or more interventions. Any network of treatments consisting of strictly unclosed loops can be thought of as a series of ITCs (**Appendix Figure 1, A and B**). In mixed treatment comparisons, both direct and indirect information is available to inform the effect size estimates for at least some of the comparisons; visually, this is shown by closed loops in a network graph (**Appendix Figure 1, C**). Closed loops are not required to be present for every comparison under study. "Network meta-analysis" is an inclusive term that incorporates the scenarios of both indirect and mixed treatment comparisons.

Network geometry evaluation: The description of characteristics of the network of interventions, which may include use of numerical summary statistics. This does not involve quantitative synthesis to compare treatments. This evaluation describes the current evidence available for the competing interventions to identify gaps and potential bias. Network geometry is described further in **Appendix Box 4**.

Appendix Box 1. The Assumption of Transitivity for Network Meta-Analysis

Methods for indirect treatment comparisons and network meta-analysis enable learning about the relative treatment effects of, for example, treatments A and B through use of studies where these interventions are compared against a common therapy, C.

When planning a network meta-analysis, it is important to assess patient and study characteristics across the studies that compare pairs of treatments. These characteristics are commonly referred to as *effect modifiers* and include traits such as average patient age, gender distribution, disease severity, and a wide range of other plausible features.

For network meta-analysis to produce valid results, it is important that the distribution of effect modifiers is similar, for example, across studies of A versus B and A versus C. This balance increases the plausibility of reliable findings from an indirect comparison of B versus C through the common comparator A. When this balance is present, the assumption of transitivity can be judged to hold.

Authors of network meta-analyses should present systematic (and even tabulated) information regarding patient and study characteristics whenever available. This information helps readers to empirically evaluate the validity of the assumption of transitivity by reviewing the distribution of potential effect modifiers across trials.

Appendix Box 2. Differences in Approach to Fitting Network Meta-Analyses

Network meta-analysis can be performed within either a frequentist or a Bayesian framework. Frequentist and Bayesian approaches to statistics differ in their definitions of probability. Thus far, the majority of published network meta-analyses have used a Bayesian approach.

Bayesian analyses return the posterior probability distribution of all the model parameters given the data and prior beliefs (e.g., from external information) about the values of the parameters. They fully encapsulate the uncertainty in the parameter of interest and thus can make direct probability statements about these parameters (e.g., the probability that one intervention is superior to another).

Frequentist analyses calculate the probability that the observed data would have occurred under their sampling distribution for hypothesized values of the parameters. This approach to parameter estimation is more indirect than the Bayesian approach.

Bayesian methods have been criticized for their perceived complexity and the potential for subjectivity to be introduced by choice of a prior distribution that may affect study findings. Others argue that explicit use of a prior distribution makes transparent how individuals can interpret the same data differently. Despite these challenges, Bayesian methods offer considerable flexibility for statistical modeling.
In-depth introductions to Bayesian methods and discussion of these and other issues can be found elsewhere.

Appendix Box 3. Network Meta-Analysis and Assessment of Consistency

Network meta-analysis often involves the combination of direct and indirect evidence. In the simplest case, we wish to compare treatments A and B and have 2 sources of information: direct evidence via studies comparing A versus B, and indirect evidence via groups of studies comparing A and B with a common intervention, C. Together, this evidence forms a closed loop, ABC.

Direct and indirect evidence for a comparison of interventions should be combined only when their findings are similar in magnitude and interpretation. For example, for a comparison of mortality rates between A and B, an odds ratio determined from studies of A versus B should be similar to the odds ratio comparing A versus B estimated indirectly based on studies of A versus C and B versus C. This assumption of comparability of direct and indirect evidence is referred to as *consistency* of treatment effects.

When a treatment network contains a closed loop of interventions, it is possible to examine statistically whether there is agreement between the direct and indirect estimates of intervention effect.

Different methods to evaluate potential differences in relative treatment effects estimated by direct and indirect comparisons are grouped as *local approaches* and *global approaches.* Local approaches (e.g., the Bucher method or the node-splitting method) assess the presence of inconsistency for a particular pairwise comparison in the network, whereas global approaches (e.g., inconsistency models, I^2 measure for inconsistency) consider the potential for inconsistency in the network as a whole.

Tests for inconsistency can have limited power to detect a true difference between direct and indirect evidence. When multiple loops are being tested for inconsistency, one or a few may show inconsistency simply by chance. Further discussions of consistency and related concepts are available elsewhere.
Inconsistency in a treatment network can indicate lack of transitivity (see **Appendix Box 1**).

Appendix Box 4. Network Geometry and Considerations for Bias

The term *network geometry* is used to refer to the architecture of the treatment comparisons that have been made for the condition under study. This includes what treatments are involved in the comparisons in a network, in what abundance they are present, the respective numbers of patients randomly assigned to each treatment, and whether particular treatments and comparisons may have been preferred or avoided.

Networks may take on different shapes. Poorly connected networks depend extensively on indirect comparisons. Meta-analyses of such networks may be less reliable than those from networks where most treatments have been compared against each other.

Qualitative description of network geometry should be provided and accompanied by a network graph. Quantitative metrics assessing features of network geometry, such as *diversity* (related to the number of treatments assessed and the balance of evidence among them), *co-occurrence* (related to whether comparisons between certain treatments are more or less common), and *homophily* (related to the extent of comparisons between treatments in the same class versus competing classes), can also be mentioned.

Although common, established steps for reviewing network geometry do not yet exist, however examples of in-depth evaluations have been described related to treatments for tropical diseases and basal cell carcinoma and may be of interest to readers. An example based on 75 trials of treatments for pulmonary arterial hypertension (**Appendix Figure 3**) suggests that head-to-head studies of active therapies may prove useful to further strengthen confidence in interpretation of summary estimates of treatment comparisons.

Appendix Box 5. Probabilities and Rankings in Network Meta-Analysis

Systematic reviews incorporating network meta-analyses can provide information about the hierarchy of competing interventions in terms of treatment rankings.

The term *treatment ranking probabilities* refers to the probabilities estimated for each treatment in a network of achieving a particular placement in an ordering of treatment effects from best to worst. A network of 10 treatments provides a total of 100 ranking probabilities—that is, for each intervention, the chance of being ranked first, second, third, fourth, fifth, and so forth).

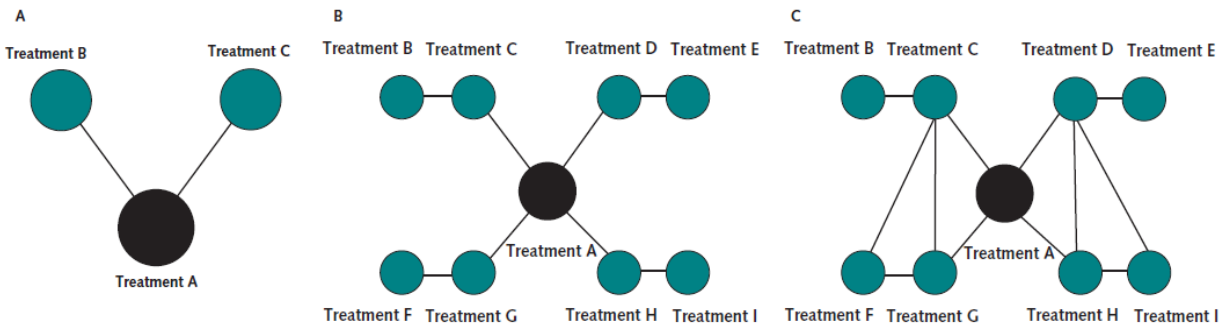
Several techniques are feasible to summarize relative rankings, and include graphical tools as well as different approaches for estimating ranking probabilities. **Appendix Figure 6** shows 2 approaches to presenting such information, on the basis of a comparison of adjuvant interventions for resected pancreatic adenocarcinoma.

Robust reporting of rankings also includes specifying median ranks with uncertainty intervals, cumulative probability curves, and the surface under the cumulative ranking (SUCRA) curve.

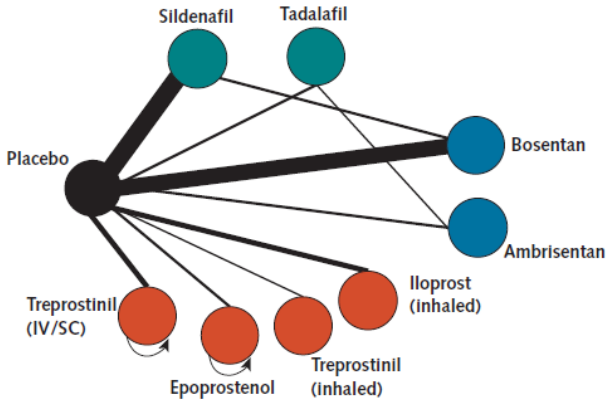
Rankings can be reported along with corresponding estimates of pairwise comparisons between interventions. Rankings should be reported with probability estimates to minimize misinterpretation from focusing too much on the most likely rank.

Rankings may exaggerate small differences in relative effects, especially if they are based on limited information. An objective assessment of the strength of information in the network and the magnitude of absolute benefits should accompany rankings to minimize potential biases.

Appendix Figure 1A-1C

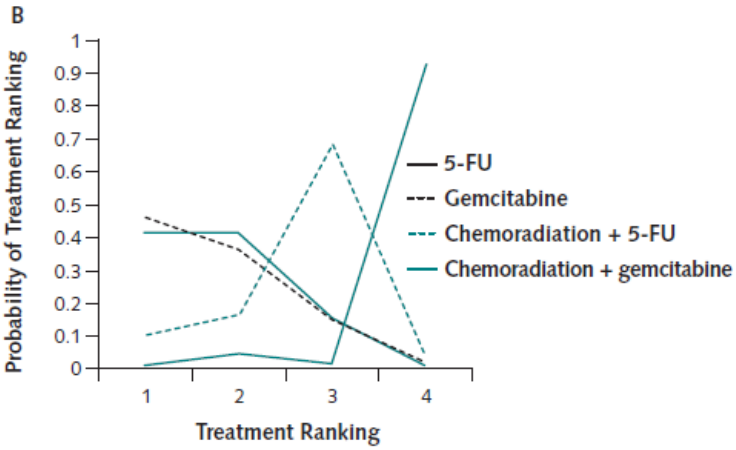


Appendix Figure 3



Appendix Figure 6

Ranking	Treatment and Cooresponding Ranking Probabilities Grade 3 or 4 Hematologic Toxicity			
	5-FU	Gemcitabine	Chemoradiation + 5-FU	Chemoradiation + gemcitabine
1	0.42	0.42	0.15	0.01
2	0.46	0.36	0.15	0.02
3	0.10	0.17	0.68	0.04
4	0.02	0.05	0.02	0.93



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Chapter 4

Impact of a Multicomponent Digital Therapeutic Mobile App on Medication Adherence in Patients with Chronic Conditions: Retrospective Analysis

Wiecek E, Torres-Robles A, Cutler RL, Benrimoj SI, Garcia-Cardenas V
Impact of a Multicomponent Digital Therapeutic Mobile App on Medication Adherence in Patients with Chronic Conditions: Retrospective Analysis
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Background:

Strategies to improve medication adherence are widespread in the literature; however, their impact is limited in real practice. Few patients persistently engage long-term to improve health outcomes, even when they are aware of the consequences of poor adherence. Despite the potential of mobile phone apps as a tool to manage medication adherence, there is still limited evidence of the impact of these innovative interventions. Real-world evidence can assist in minimizing this evidence gap.

Objective:

The objective of this study was to analyze the impact over time of a previously implemented digital therapeutic mobile app on medication adherence rates in adults with any chronic condition.

Methods:

A retrospective observational study was performed to assess the adherence rates of patients with any chronic condition using Perx Health, a digital therapeutic that uses multiple components within a mobile health app to improve medication adherence. These components include gamification, dosage reminders, incentives, educational components, and social community components. Adherence was measured through mobile direct observation of therapy (MDOT) over 3-month and 6-month time periods. Implementation adherence, defined as the percentage of doses in which the correct dose of a medication was taken, was assessed across the study periods, in addition to timing adherence or percentage of doses taken at the appropriate time (±1 hour). The Friedman test was used to compare differences in adherence rates over time.

Results:

We analyzed 243 and 130 patients who used the app for 3 months and 6 months, respectively. The average age of the 243 patients was 43.8 years (SD 15.5), and 156 (64.2%) were female. The most common medications prescribed were varenicline, rosuvastatin, and cholecalciferol. The median implementation adherence was 96.6%

(IQR 82.1%-100%) over 3 months and 96.8% (IQR 87.1%-100%) over 6 months. Nonsignificant differences in adherence rates over time were observed in the 6-month analysis (Fr(2)=4.314, *P*=.505) and 3-month analysis (Fr(2)=0.635, *P*=.728). Similarly, the timing adherence analysis revealed stable trends with no significant changes over time.

Conclusions:

Retrospective analysis of users of a medication adherence management mobile app revealed a positive trend in maintaining optimal medication adherence over time. Mobile technology utilizing gamification, dosage reminders, incentives, education, and social community interventions appears to be a promising strategy to manage medication adherence in real practice.

Keywords: medication adherence; medication compliance; mobile phone; mobile apps; mHealth; gamification

Introduction

Strategies to manage medication adherence, which is defined as the process by which patients take their medications as prescribed [1], are widespread in the literature and are reported to be modestly effective [2]. Most likely due to the multidimensional nature of medication-taking behavior and numerous determinants of nonadherence [3], multicomponent interventions with both technical and educational aspects have shown the most success [4]. However, these strategies have failed to find success in the real world; patient adherence levels tend to decrease in the long term and stay consistently at around 50% [5]. These strategies are limited not only by the capacity of the health care system delivering them but also by low levels of patient engagement. Even when patients are aware of the risks and consequences of diseases, few engage persistently in therapies to improve health outcomes [6-8].

Cognitive biases resulting in irrational and unhealthy behavior may be a key contributor to patient engagement in preventative health strategies. In contrast with traditional economic models of rational choice, modern insights have suggested that human behavior is highly influenced by the context or environment of our decision-making process rather than by price signals or factual information [9]. The field of behavioral economics combines psychology and neoclassical economics to shed light on the errors in mental processing that prevent patients from making rational and beneficial decisions to improve their health [10]. Some health behaviors may require high levels of self-control, meaning that a patient may need to endure "certain and immediate inconveniences in return for uncertain and distant benefits [11]." Obvious behaviors that create this paradigm are healthy food choices and exercise [12]. However, medication adherence, or the act of taking a medication at a certain time each day, creates inconvenience by disrupting the patient's daily lifestyle or causing adverse effects; meanwhile, this behavior is only rewarded with uncertain and distant future health outcomes.

Strategies to influence cognitive biases include incentives and rewards. Incentives and rewards not only impact motivation but also create an immediate benefit to counteract inconvenience [13]. In previous literature, financial incentives showed success in improving medication adherence but were limited by long-term viability and capacity of resources, with economic incentives often eroding the potential economic gain [13-19]. The use of lottery-based incentives has also shown success in sustainment of adherence and long-term engagement [20,21]. Frequent lotteries with small rewards can engage patients based on regret aversion, namely the understanding that the emotional cost of regret (ie, missing a reward by not taking a medication dose) is significant [21].

Methods of gamification or use of nonfinancial extrinsic motivators, such as accruing "points," can be feasible and practical ways to create similar senses of gratification and motivation [22]. Gamification is the application of game elements for purposes other than their expected use for entertainment [23]. An individual's choice to engage in an activity is affected by extrinsic and intrinsic motivation. Medication adherence requires intrinsic motivation driven by internal rewards; this sense of motivation can often be difficult to achieve for behavior that has uncertain and distant health benefits. Through the use of gamification, extrinsic motivators such as earning points and monetary rewards can create and trigger internal motivation [23]. Gamification is not only able to use both extrinsic and intrinsic motivation to create consistent engagement through rewards, such as points or daily streaks, but can also create a sense of achievement [23]. Both gamification and rewards appear to be promising strategies to potentiate the effects of frequently used adherence management approaches, such as educational components and reminders.

Currently, over 300,000 mobile health (mHealth) apps are available; they have become common and instrumental tools for health behavior change in modern times [24,25]. Success has already been demonstrated with using mobile phone apps to support health behavior changes, ranging from constructing a healthy diet to managing chronic pain or improving physical activity [26-28]. Despite the potential of mobile phone apps as a tool to manage medication adherence, there is limited evidence of the effectiveness of these innovative interventions [29-31]. Real-world evidence, which refers to health care information gathered outside clinical research settings, can help minimize this evidence gap. Generated through the analysis of multiple sources, including electronic health records and mHealth apps, real-world evidence can be used to test how health interventions work in usual practice [32]. Observational studies of real-world data can assist in evaluating the potential impact of implemented health interventions in real world settings, such as interventions delivered through mobile phone apps [33].

The objective of this study was to use real-world data to analyze the impact over time of a previously implemented digital therapeutic mobile app on medication adherence rates in adults with any chronic condition. The impact on timing adherence rates was also analyzed.

Methods

Study design

This was a retrospective observational study using real-world data. The implementation adherence of people in Australia using a commercially available smartphone application, Perx, was evaluated. The ESPACOMP Medication Adherence Reporting Guideline (EMERGE) and STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) Statement were used [1,34].

Intervention: Perx Digital Therapeutic

Perx is a digital therapeutic that uses different components within a mobile app to improve adherence to medications. These include technical components (through dosage reminders based on the individual patient's dosing regimen and individualized visual adherence feedback), educational components (through the use of educational materials on the disease and medications used), incentives and rewards (lottery-style delivery of gift cards), a social community (through a chat forum and collaborative competition dynamics), and gamification (through the use of point-earning and minigames to enhance the medication-taking experience). Perx enables users to input their medication schedule information while sending dosage reminders based on the individual patient's regimen. Doses taken are self-reported and recorded by mobile direct observation of therapy (MDOT) photo verification [35]. "Gold" points are rewarded to users for each dose taken on time (±1 hour). Additionally, different minigames are offered at the time of a medication dose to enhance the medication-taking experience. The patient can earn extra gold points through learning a daily fact about their medication or disease state and by completing all daily tasks. Supplementary tasks within the app include health measurements, appointment reminders, physical therapy sessions, and other health actions, which provide users with a comprehensive system to track their health in addition to visual adherence feedback on their personal progress. A social forum and leaderboard component are also included, which create a Perx community. Reward shopping vouchers for popular stores can be redeemed either with a certain amount of gold earned or randomly by taking a correct dose. Screenshots showing the different features of the app can be found in Multimedia Appendix 1.

Data Source and Patients

Deidentified user data from the Perx database were analyzed for this study to assess adherence dosing data between October 2018 and May 2019 within Australia. All information was deidentified, including medications, doses, schedules, user age, dosages taken and missed, and timestamps of dosages taken.

Users were recruited to use the app via a range of channels, including patient advocacy organizations (ie, Cystic Fibrosis Australia and Diabetes NSW & ACT), local community pharmacies, outpatient clinics at local hospitals, and app stores. App users with any chronic condition were included in the analysis. Two user cohorts were analyzed: one for users who used the app consistently for over 6 months and one for users who used the app consistently for 3 months. Users were excluded from the analysis if they used the intervention for less than 30% of the time period defined by the number of days active on the app. The 30% threshold was used because it excluded patients who appeared to decide to stop using the app during the time period of the analysis, as the objective was to analyze user medication adherence rather than adherence to the app itself.

A subanalysis of timing adherence was also performed for both time periods. Users were excluded from the subanalysis if timestamps were not available for the entire time period.

Outcome: Medication Adherence

Adherence implementation rates (where adherence implementation was defined as the extent to which a patient's actual dosing corresponded to the prescribed dosing regimen [1]) were calculated by dividing doses taken by total doses scheduled per 30-day period. This included doses taken outside the ±1-hour time period and was verified by comparing the recorded timestamps to the dosing schedules inputted within the app.

For the subanalysis, timing adherence was assessed with doses taken at the correct time (±1 hour) over total doses scheduled per 30-day period. This additional analysis was performed to understand the effects of the incentives, as users could only redeem incentives if the medication was taken within the ±1 hour time threshold. Both adherence measures are presented as percentages. Rates were compared to an optimal adherence level of 80%, which is the most commonly used cutoff point in the literature [36,37].

Data Analysis

Data were analyzed by integrating the PROC SQL (SAS University Edition 9.4) and Python (Jupyter Lab 1.0) language programs and Microsoft Excel 2019 (Microsoft Corporation) to organize and retrieve the results. The analysis was conducted in 30-day time periods. Study variables were summarized using mean (SD) and median (IQR). Adherence variables were verified for normal distribution using the Shapiro-Wilk test. Due to the distribution of the data, the Friedman test was used to compare differences in adherence rates over time. A P value <.05 was considered to indicate statistical significance.

Ethics Statement

The University of Technology Sydney Human Research Ethics Committee (HREC) approved this study (ETH19-3622). All users recruited into the program were required

to actively accept and consent to the Terms of Use and Privacy Policy, which stated that de-identified data in aggregated form may be used by third parties for research and other purposes. No personal or confidential data were included in the database; therefore, informed patient consent was not required.

Results

Study Sample

A total of 130 users were included in the 6-month analysis, and 243 users were included in the 3-month analysis. For the timing adherence subanalysis, 111 users and 221 users were included in the 6-month and 3-month analyses, respectively.

6-Month Analysis Group

The distribution of users according to gender was 36/130 male (27.7%) and 88/130 (67.7%); 6/130 users (4.6%) did not disclose their gender. The average age was 45.8 years (SD 17.2). The most common medications prescribed were rosuvastatin, cholecalciferol, and atorvastatin; the mean number of medications prescribed per patient was 4.3 (SD 3.1).

3-Month Analysis Group

The distribution of users according to gender was 80/243 male (32.9%) and 156/243 female (64.2%); 7/243 users (2.9%) did not disclose their gender). The average age was 43.8 years (SD 15.5). The most common medications prescribed were varenicline, rosuvastatin, and cholecalciferol; the mean number of medications prescribed per patient was 4.0 (SD 2.9).

Implementation Adherence

Adherence rates across the 6-month time period are shown in Table 1. The overall median implementation adherence was 96.8% (IQR 87.1%-100%) across 6 months. A small decreasing trend was observed from month 4 to month 6. However, the Friedman test revealed non-significant differences in adherence rates over time (Fr(2)=4.314, P=.505) (Figure 1).

Adherence rates across the 3-month time period are shown in Table 1. The overall median implementation adherence was 96.6% (IQR 82.1%-100%) across 3 months. A slight decreasing trend was seen from month 1 to month 3 (Figure 2). Similarly to the 6-month analysis, nonsignificant differences in adherence rates over time were found (Fr(2)=0.635, P=.728).

Timing Adherence Sub-analysis

Timing adherence rates across study time periods can be found in Table 2. For the 111 users included in the 6-month timing adherence analysis, their adherence remained unchanged, with medians of 77.3% (IQR 52.0%-93.1%) in month 1 and 77.4% (IQR 36.2%-94.4%) in month 6. The median value across the time periods was 79.0% (IQR 50.8%-92.9%). Overall, there were no significant changes over time (Fr(2)=5.465, P=.362) (Figure 3).

In the 3-month timing adherence analysis, 221 users' adherence remained stable (Table 2), with nonsignificant changes across time periods (Fr(2)=2.125, P=.346) (Figure 4).

Table 1. Adherence rates across the 6-month and 3-month time periods.

Study period	Mean (SD)	Median (IQR)
6-month analysis (%)		
Month 1	88.6 (21.5)	96.8 (88.0-100)
Month 2	88.0 (20.3)	96.8 (82.5-100)
Month 3	89.5 (18.5)	97.1 (87.1-100)
Month 4	88.6 (20.9)	98.3 (86.5-100)
Month 5	87.0 (24.0)	97.1 (85.7-100)
Month 6	83.9 (26.9)	96.8 (83.9-100)
Overall	87.6 (16.9)	96.8 (87.1-100)
3-month analysis (%)		
Month 1	87.3 (21.1)	96.1 (86.1-99.6)
Month 2	84.1 (24.7)	96.8 (79.0-100)
Month 3	82.5 (27.5)	96.7 (80.6-100)
Overall	84.6 (20.9)	96.6 (82.1-100)

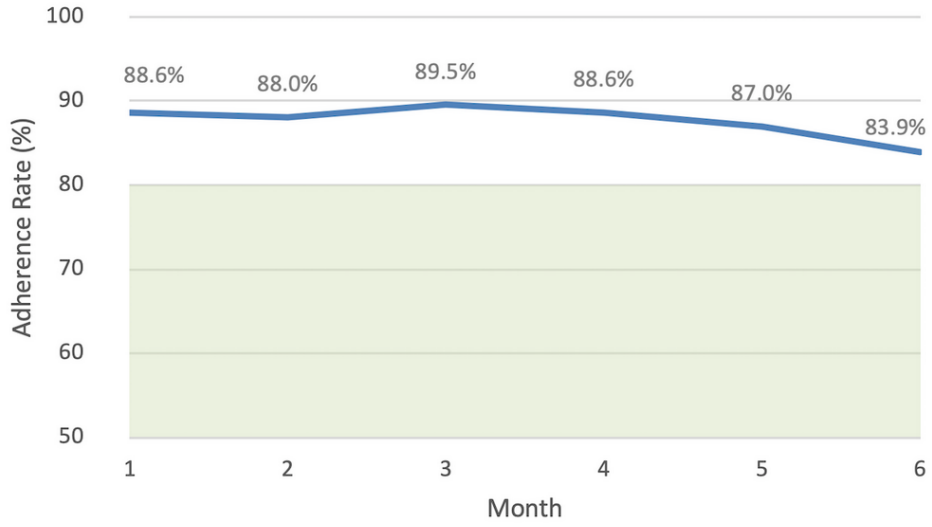


Figure 1. Mean implementation adherence rates of 130 users of the Perx app over 6 months. The shaded area below 80% indicates less than optimal adherence based on the literature.

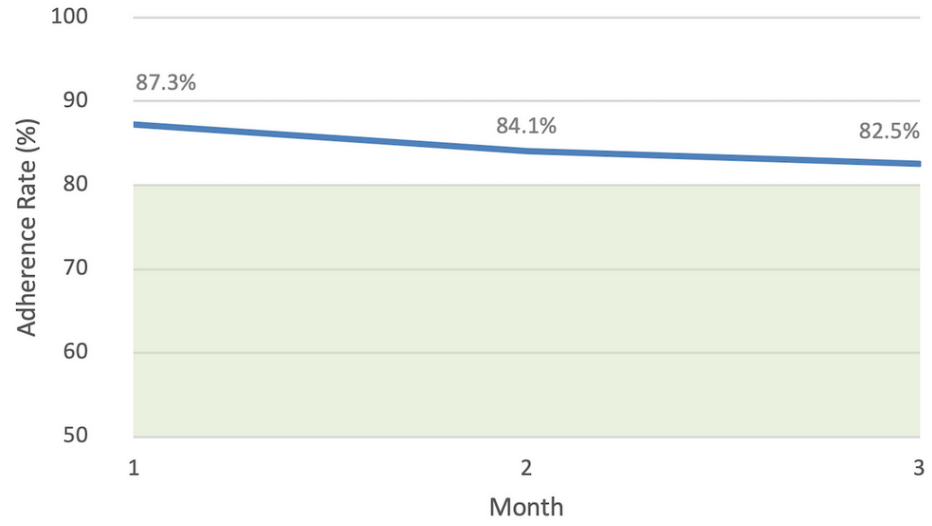


Figure 2. Mean implementation adherence rates of 243 users of the Perx app over 3 months. The shaded area below 80% indicates less than optimal adherence based on the literature.

Table 2. Timing adherence across the 6-month and 3-month time periods.

Study period	Mean (SD)	Median (IQR)
6-month analysis (%)		
Month 1	68.4 (27.9)	77.3 (52.0-93.1)
Month 2	70.5 (28.4)	82.3 (54.8-91.9)
Month 3	69.2 (27.7)	79.8 (50.3-93.5)
Month 4	69.8 (28.8)	81.7 (51.4-93.5)
Month 5	68.7 (28.9)	80.6 (52.8-92.7)
Month 6	63.4 (33.7)	77.4 (36.2-94.4)
Overall	68.5 (29.1)	79.0 (50.8-92.9)
3-month analysis (%)		
Month 1	63.7 (28.2)	71.0 (46.4-85.9)
Month 2	64.0 (30.8)	74.2 (41.9-90.3)
Month 3	61.4 (32.3)	71.0 (34.7-88.7)
Overall	61.1 (28.5)	72.0 (41.8-88.3)

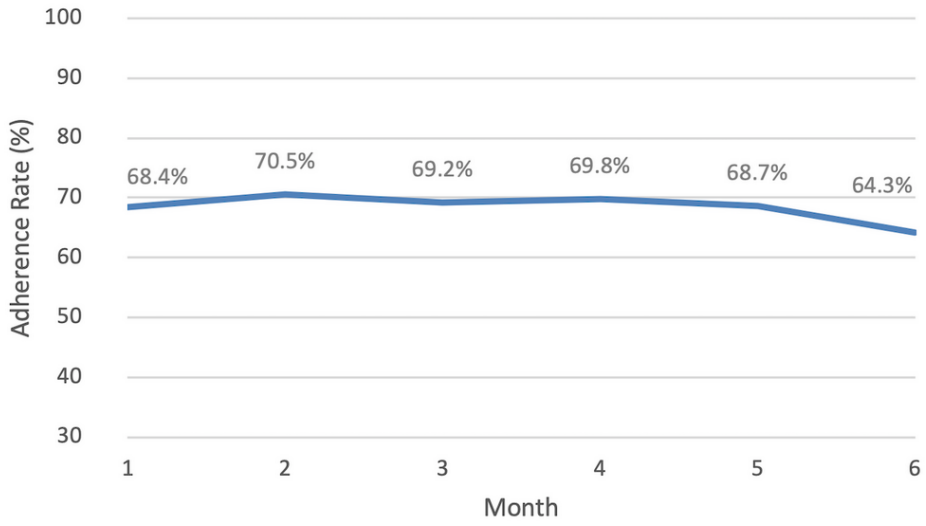


Figure 3. Mean timing adherence rates of 111 users of the Perx app over 6 months. The users were considered to be adherent to the dose if it was taken within ±1 hour of the scheduled time.

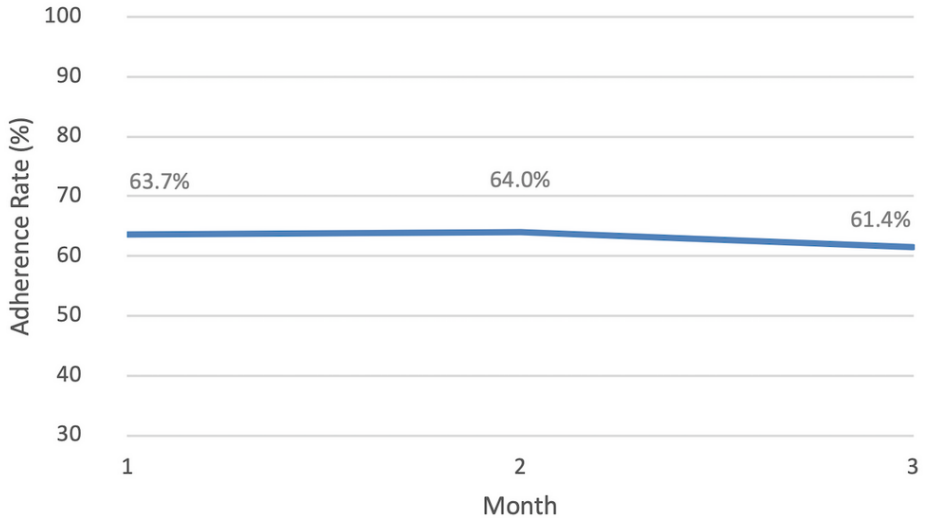


Figure 4. Mean timing adherence rates of 221 users of the Perx app over 3 months. The users were considered to be adherent to the dose if it was taken within ±1 hour of the scheduled time.

Discussion

Principal Findings

Retrospective analysis of the medication adherence of users receiving a multicomponent adherence management intervention that includes reminders, educational components, incentives, gamification, and social community components demonstrated that this intervention is a successful approach to maintaining optimal medication adherence. To our knowledge, this is the first study investigating a comprehensive multicomponent mobile intervention to maintain medication adherence across different chronic conditions.

Trends observed from the users of the mobile app showed high rates of adherence across the study periods. The adherence rates of Perx users averaged over 85% across six months. This was significantly higher than previously observed dispensing data adherence rates in Australian patients, which were found to be between 50.2% and 66.9% [38]. While a slight decrease in adherence was observed over 6 months, the long-term rates remained above 80%, which is often considered to be an optimal threshold for medication adherence [36]. The decrease in adherence rates was found to be statistically insignificant [36][39]. The gradual decrease was less pronounced than that in previous literature examining the long-term effects and multidimensional, dynamic nature of medication adherence; in a previous study, average adherence was estimated to decrease by 1.1% per month [40]. This suggests that the addition of gamification and incentive components to more traditional management interventions (eg, educational components and reminders) is a viable option to inspire long-term motivation and adherence to medications.

A recent network meta-analysis examined the impact of adherence interventions across time and identified multicomponent interventions as the most effective long-term solution [4]. Although there is limited evidence, interventions that include incentives and technical aspects (ie, dosage reminders) have been shown to be the most effective in sustaining long-term results [4]. The Perx digital therapeutic presents an advantageous alternative to existing medication adherence interventions due to its incorporation of multiple and innovative components into one platform to continuously motivate and empower users. A main component of the Perx app, medication reminders, has long been identified as a successful intervention component to improve adherence [41,42]. However, although medication reminders help to enhance adherence, they only affect one dimension of the multiple nonadherence determinants and are frequently used in combination with additional interventions, such as education [4]. Educational interventions are also a common long-term strategy to improve adherence to medications [2,43]. Delivered by numerous methods, these interventions can be moderately effective; however, they are not a sole solution to improve adherence for all patients [44]. When combined with technical and attitudinal components such as motivational interviewing, education-based strategies are found to be even more successful [4].

Motivation is another common determinant of medication adherence [3]. Patients can be fully aware of the positive health benefits medications provide as well as the consequences of poor health behavior; however, some patients consistently make poor health choices [11]. Present-biased preferences explain the "human tendency to grab immediate rewards and to avoid immediate costs in a way that our 'long-run selves' do not appreciate [10]." An individual may analyze immediate costs or immediate rewards to make a decision; such decisions often result from impatience or immediate gratification and place greater value on achieving gratification in the present moment than obtaining the same reward in the future. Positive and negative health outcomes remain too distant of a reward and consequence, respectively [45]. The Perx digital therapeutic aims to create instant gratification through gamification elements. Through receiving instant praise and reward after each medication dose taken on time, users may be motivated to continue to be adherent. Motivation can additionally be created through intrinsic forces, as stated by the self-determination theory. The self-determination theory suggests that the nature of perceptible motivational types determines the predictability and force of how people behave, rather than the amount of motivation [46,47]. Therefore, it is necessary for gamified systems to promote a sense of autonomy, competence, and relatedness to create the intrinsic motivation needed to continue the value of the extrinsic motivating factors [46,48]. The Perx digital therapeutic intervention may be successful because it meets the users' need for competence, autonomy, and relatedness. Competence and autonomy are created by setting challenging yet manageable goals, where adherence is the challenge and financial incentives are the goals. Users can also follow their progress through points, leaderboards, and personal visualized feedback graphs on their individual adherence. This feedback provides additional positive reinforcement and has been proven to be a successful component of interventions to improve medication adherence; it is estimated that adherence increases 8.8% for interventions where feedback is included compared to those that do not include feedback [40,49]. The social community component meets

the need for relatedness by fostering a feeling of belonging to a community that shares the common goal of better health [46].

While gamification is a main force in creating motivation in the app, the impact of rewards and incentives cannot be dismissed. The use of incentives in public policy has long been used as an extrinsic force to influence behavior and intrinsic motivation [9,50,51]. However, the use of incentives to encourage health behaviors is relatively new, and more research is needed in this area. Financial incentives have proven to improve medication adherence in certain populations; however, their long-term viability can be questioned due to the resources needed [13-19]. Although incentives can be critiqued on their superficial nature or short-term viability, they may be a powerful motivating factor in creating habit-based behavior, a proven successful key in improving medication adherence, and an intrinsic source of motivation [51,52]. In the case of Perx, the extrinsic nature of the incentives may create habit-based adherence behavior in addition to intrinsic motivation to improve health outcomes. Additionally, the Perx app uses lottery-based incentives rather than predictable rewards. These incentives can enhance health behavior based on regret aversion or the human tendency to place a significant cost on regret [20]. If users believe that missing a medication dose can prevent them from winning a reward, they are still likely to improve their adherence, even without a guaranteed instant reward [21].

Limitations

Although our analysis proved that the Perx digital therapeutic is an effective intervention in managing medication adherence, it does have some limitations. First, the number of app users with available data was limited, did not extend past 6 months for the majority of users, and did not include information on the users' clinical conditions. Due to this, we were unable to perform subanalyses based on patient age, gender, medication, or condition. Second, we could not establish baseline adherence rates before the

intervention was implemented or evaluate a control group due to the retrospective nature of the study. Third, while we believe that our sample reflects an accurate sample of patients who would be likely to use a mobile app to manage medications, the users who downloaded the app may also have been likely to adhere to their medications without the app. Conversely, it could also be argued that patients who need adherence management support would be more likely to download the app. Finally, while we could measure the number of active days per patient, it was not possible to determine full user engagement of the intervention in this analysis to understand the extent to which the intervention was used by each user.

Strengths

One strength of our study is our measure of adherence, self-reporting with MDOT [35]. Similar to electronic methods such as the Medication Event Monitoring System (MEMS), MDOT enables objective measurement while simultaneously providing timestamps to additionally measure timing adherence, which is an important component of the multidimensional medication-taking process [35]. Additionally, our analysis of the gamification of mobile apps to maintain positive health behaviors is part of a new and emerging research landscape within the pharmacy and health care sector that has not been previously examined [53]. With the increasing number of health apps entering the market, supportive evidence is necessary to demonstrate the effectiveness of these tools and to indicate whether they should be recommended by health care professionals as a component of medication therapy [54,55]. Finally, our use of real-world data generated from users of this commercially available mobile app was a strength in that the data can be applied to a broader population of patients and reflect actual use in practice [32].

Future Work

A 12-month clinical trial is currently being conducted with the objective of assessing the efficacy of the Perx intervention in adherence and clinical outcomes. Future research

should aim to assess the effectiveness of this intervention in improving adherence to medications and other gamification- or incentive-based strategies in addition to observing the impact on clinical health outcomes. Furthermore, a longer analysis period of 12 to 24 months would be beneficial in observing the long-term effects to determine if these types of interventions can sustain gold-standard adherence rates above 80% for longer than 6 months. It would additionally be useful to analyze the impact of the intervention across different points in the medication-taking process, such as initiation of medication, implementation and persistence adherence, and time to discontinuation of medication [1]. Finally, the opinions of stakeholders, specifically users, regarding the app and intervention components are vital to understand the main motivating factor in promoting adherence. A full engagement analysis identifying the components of the app on which the most time is spent as well as a user survey analysis are required to obtain a complete understanding of the success of the intervention.

Conclusion

Retrospective analysis of a digital therapeutic mobile app that merges gamification, education, reminders, a social community, and incentive-based components indicates that this intervention is successful in maintaining optimal medication adherence over time. Extrinsic external monetary motivators combined with fundamental game mechanics and other common behavioral change components may be a key force to promote intrinsic motivation and habit-based behavior, which can spark long-term changes in health behavior. Future research should evaluate the long-term impact of mobile apps using these components over a longer time period using experimental designs.

Acknowledgements

We would like to thank Lucky Health Pty Ltd for providing the data. This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

M-DOT: Mobile Direct Observation of Therapy

EMERGE: ESPACOMP Medication Adherence Reporting Guideline

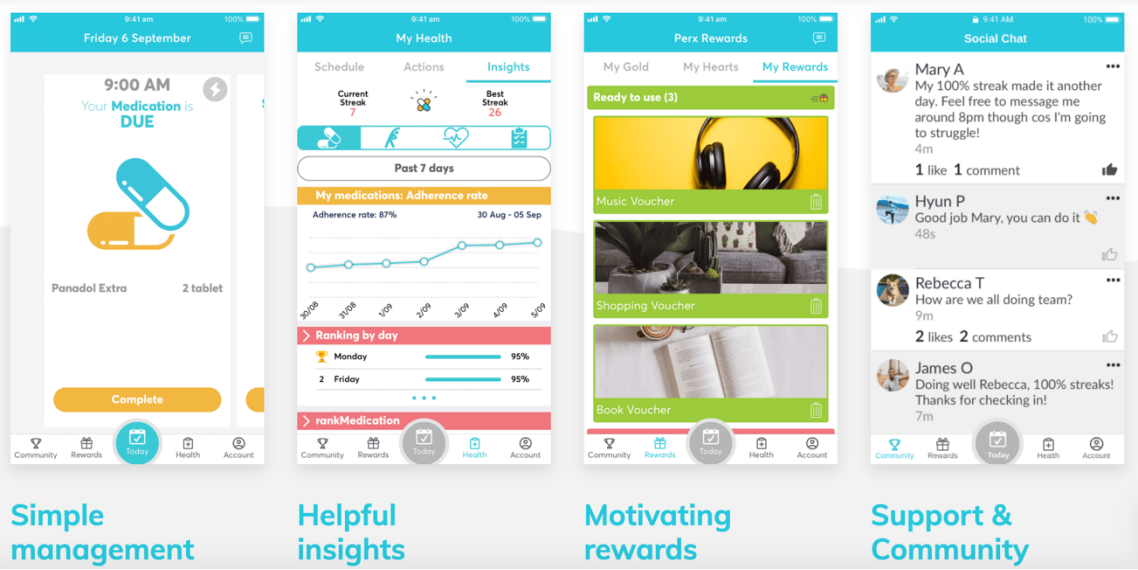
STROBE: STrengthening the Reporting of OBservational Studies in Epidemiology

SD: Standard Deviation

HREC: Human Research Ethics Committee

Multimedia Appendix 1

Screenshots of the most important features of the Perx app.



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Chapter 5

User Perception of a mHealth Application Using Gamification and Incentives to Improve Medication Adherence: Content Analysis of User Survey Reviews

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Introduction

MHealth (mobile health) is in an advantageous position to enhance the management of medication adherence. Rewards and gamification are two innovative techniques being utilised to combat the perception of medication adherence as an inconvenience. Perx Health is an mHealth app aiming to improve adherence to medications by utilising these strategies along with reminders. While it has proven effectiveness in enhancing adherence, its acceptability by its users is still unknown. The aim of this study was to analyse user beliefs, perceptions and experiences towards an already implemented mHealth app utilising multiple components including rewards, reminders and gamification.

Methods

Retrospective mixed methods analysis of quantitative survey and qualitative cross-sectional questionnaire data obtained from Perx users was used. Raw qualitative data was organised, cleaned and imported into NVivo version 12. A sample of data (n = 200) was tested by two researchers and common words were extracted to design categories. Content analysis was conducted between two researchers to code responses into overarching categories by identifying common phrases and words embedded within user survey responses. Quantitative data was analysed using Microsoft Excel.

Results

The majority 88.9% of user responses (88.9%) stated that they were likely to recommend Perx. Common frequent positive reasons as to why users would recommend Perx included having an overall positive experience, improved medication adherence, appreciating the reminder features and the inclusion of rewards. Common negative reasons as to why users would not recommend Perx included reward frequency, an overall negative experience, reward type, technology functionality and repetitive educational material. Components of Perx thought to require improvement was rewards, games and educational material. However, a large number of patients thought Perx did not require improvement or stated it was already a positive experience.

Conclusion

The use of an mHealth app utilising rewards, reminders and gamification is an intervention that is widely accepted by its users. Patients enjoyed and would recommend the application overall, but especially appreciated reminder features and stated that the improved their medication

adherence. To improve the app, users would like higher reward frequency, functionality issues such as glitches to be eliminated and updated educational material.

Introduction

The popularity of mobile health (mHealth), or medical and public health practice supported by mobile devices, has grown worldwide with an estimated two billion smartphone users identified in 2018.[1] This expansion provides opportunities to utilise these mobile technologies to address challenges within the health care system such as medication non-adherence.[2] With the potential health solutions that mobile applications could provide, it is not surprising that there are over 97,000 mobile health applications available on various application platforms and were 3.7 billion downloads of mHealth mobile applications in 2017.[1]

Mobile tools have been advantageous in improving access to health care, delivering medical information and data in a cost-effective manner, and improving clinical health outcomes through health behaviour change.[3] In a recent classification, six main uses were defined for mHealth interventions based on content of current mobile apps available: obtaining educational tools, consulting medical information and references, fulfilling a contextual need, communication and/or sharing information, managing health professionals' activities, and facilitating health-related management of patients.[4] Employing these uses in mHealth, a specific opportunity to improve clinical health outcomes includes medication adherence, or "the process by which patients take their medications as prescribed."[5] Non-adherence to medications, or not taking medication as prescribed, limits the capabilities and optimization of therapy benefits in improving health outcomes. Causing increased rehospitalisations, increased morbidity and mortality, and higher healthcare costs, non-adherence has been declared by the World Health Organization as an epidemic with only 50% of chronic disease patients revealed adherent.[2, 6-8] Having multiple determinants, adherence is a complicated issue most effectively improved by interventions with multiple components.[9] MHealth is becoming a rapidly popular tool to address this problem.[10]

The fast integration and development of mobile tools to improve and monitor our health has left a major gap in understanding users' opinions of the rapidly changing health management technologies. Content analyses of mHealth features, usability testing of apps' functioning, and observational studies exploring use and connection to clinical outcomes have been used to better understand these digital tools' effectiveness.[11, 15] Previous literature has also examined

the relevance of mHealth solutions as well as the implementation and healthcare professionals' perspective. Yet even with understanding the effectiveness of these tools, limited knowledge is available on the main stakeholders' opinion: the users themselves. A recent meta-ethnographic review identified qualitative studies reviewing patients' perception of mHealth apps and concluded patients consider mHealth apps useful, issues identified include more closely tailored designs, cost, validity of information delivered, and security and privacy issues. This review presented qualitative findings showing that mHealth apps can strengthen patient engagement in self-care.[11] Although this is the case, it has been documented that patient engagement is dependent on patient perception of an intervention as useful and facilitating improvements in health outcomes.[11] While patient perception towards other modifying health behaviours such as smoking cessation or type II diabetes management have been found to be positive,[12, 13] the patient perception towards the behaviour change of a medication adherence mHealth app remains relatively unknown. Few medication adherence mHealth apps have been examined on patient perception and the interventions of those that have remain focused on traditional methods of improving medication adherence through reminders and education.[11] Without this knowledge, we do not have an understanding of the acceptibility, desirability and patient engagement of mHealth within medication adherence.

In the uprising of mobile technologies to improve medication adherence, a specific mHealth digital therapeutic has utilised a distinctive strategy to motivate and empower patients managing their health. The Perx mobile app was found to be effective in managing medication adherence with their innovative approach through gamification concepts and monetary rewards to incite behaviour change. Though users of the Perx mobile app sustained high adherence rates over time,[14] the app's capacity to improve health outcomes will rely on its capability to engage and retain users. Additionally, given the fast integration of mHealth apps in society, it is crucial to document and explore user perceptions, beliefs, and experiences as well as establish how highly mHealth apps are appreciated.[11] By reviewing these user perspectives, it can be established whether users agree the integration of a mHealth app is feasible and desirable.[15] Therefore, it is imperative to examine user opinion and perception within the Perx mHealth app.

We aim to conduct a content analysis of user reviews to explore user's perceptions, beliefs, and experiences of Perx, an already implemented mHealth app utilising gamification and reward concepts to promote behaviour change.

Methods

Study Design

Retrospective mixed methods analysis of quantitative and qualitative survey data was used. Data was obtained from users using the smartphone app Perx aimed at analysing user satisfaction towards the application. The Consolidated criteria for Reporting Qualitative research (COREQ) guidelines were used.[16]

Intervention – Perx Health Application

Perx is a digital therapeutic offering that utilises different components within a mHealth app to motivate users and improve adherence to medications. These components include: (1) technical components (dosage reminders based on the individual patient's dosing regimen and individualised visual adherence feedback), (2) educational components (educational materials on the medication and disease), (3) incentives and rewards (lottery-based gift card system) (4) a social community (chat forum and collaborative competitive dynamics) and (5) gamification concepts (by point-earning and mini-games). Perx users input their medication schedule information and are sent dosage reminders based on the individual user's regimen. Doses taken are self- reported and recorded by mDOT photo verification. Users are rewarded with points for each dose taken on time (+/- one hour) and a lottery incentive of chance instant wins. Mini-games are offered at the time of medication dose to enhance the medication-taking experience. Additional points can be earned through educational daily facts about the patient's medication or disease state and completing all daily tasks. Points may be redeemed for shopping gift cards. Supplementary tasks within the app to manage all aspects of a user's health include health measurements (blood pressure monitoring, blood glucose monitoring, etc.), appointment reminders, physical therapy sessions, and other customisable actions in addition to visual adherence feedback on a user's progress. A social forum and collaborative competitive dynamics are also included creating a Perx community.

User satisfaction survey

Users from the Perx Health were asked 3 questions:

1. How likely are you to recommend Perx on a scale from 0 to 10, with 0 being very unlikely and 10 being very likely to recommend?
2. Why did you give Perx that score?
3. What is one thing we could improve within the app?

The satisfaction survey was based on the NPS or Net Promoter Score, the most widely used customer satisfaction survey. It is based on a single question to measure customer experience and loyalty to a product. Its original form has limitations in only asking "how is the product" without asking what could be improved or worked on. Therefore, our Perx survey analysis added an additional question, "What is one thing we could improve within the app?"

Perx users could respond multiple times to questions depending on the amount of time they used the app (once per month).

Data Source and Patients

Users from the Perx Health database in Australia were used for this study to assess user satisfaction data between November 2018 and September 2019. Users were prompted within the app with cross-sectional surveys conducted within the first two weeks of using the app and once per month thereafter, with multiple responses possible per user. All information was de-identified including user age and responses.

Data Analysis

Raw qualitative data was organised, cleaned and imported into NVivo version 12. A sample of data (n = 200) was tested and common words were extracted to design the categorical node analysis. Qualitative content analysis was conducted between two researchers to code responses into overarching categories and themes by identifying common phrases and words embedded within cross-sectional user survey responses. An inductive approach was used that followed three main coding steps: (1) initial open coding, (2) establishment of categories, and

(3) abstraction into themes. User responses could be categorised into more than one category or theme depending on the text analysis of the individual response. The question “Why did you give Perx this score?” was separated into positive, negative and neutral responses and separately coded into most suitable category with frequency examined. The question “What is the one thing we could improve within the app?” was separately coded into most suitable category and theme based on user words used in the user response, and then analysed to determine frequency. Qualitative themes were extracted from patterns found in the content analysis. All quantitative data extracted from the “How likely are you to recommend Perx on a scale from 0 to 10?” question was analysed in Microsoft Excel.

Repeat evaluation of users was analysed across time for the net promoter score (rating from 0 to 10). However, for qualitative data on survey questions 2 and 3, an analysis across time was not performed. The questions asked were open-ended to provide new insights rather than evaluate aspects of the app over time. We included multiple responses from the same user over time as the scores, experiences and answers for improvement could change over time. A sample analysis was taken on survey responses at month one versus survey responses at month 6 and no patterns of change were determined to warrant further investigation.

Ethics

University of Technology Sydney Human Research Ethics Committee (HREC) approved this study (ETH19-3622). The study was classified as having Nil/Negligible Risk. No personal or confidential data was included in the database which therefore did not require informed patient consent.

Results

Study Sample

There were 6,296 responses to the survey questions made by a total of 449 Perx application users over an 11-month period from November 2018 and September 2019. The mean number of responses per user was 4.7 (SD 3.23). All users were between the age of 18 and 67 years of age with an average age of 35 (SD).

How likely are you to recommend Perx on a scale from 0 to 10?

Of the 2,110 responses to this question 1,026 (48.6%) of responses stated that users were very likely to recommend (score of 10) Perx. For users that were likely (score of seven and above) to recommend Perx, 88.9% (1,876) gave a score of seven or higher (Figure 1). Of those unsure if they would recommend Perx, 4.2% (90) of responses gave a score of five (Figure 1). Those very unlikely to recommend Perx were 0.9% (19) of responses that gave a score of zero. In addition, 3.1% (66) of responses stated that users were unlikely (score between one and four) to recommend Perx (Figure 1). The average score given was 8.65 (SD 1.92). Of users that gave multiple responses, 346 were identified with an average first response score of 8.57 (SD 2.01) and average last response score of 8.54 (SD 1.95).

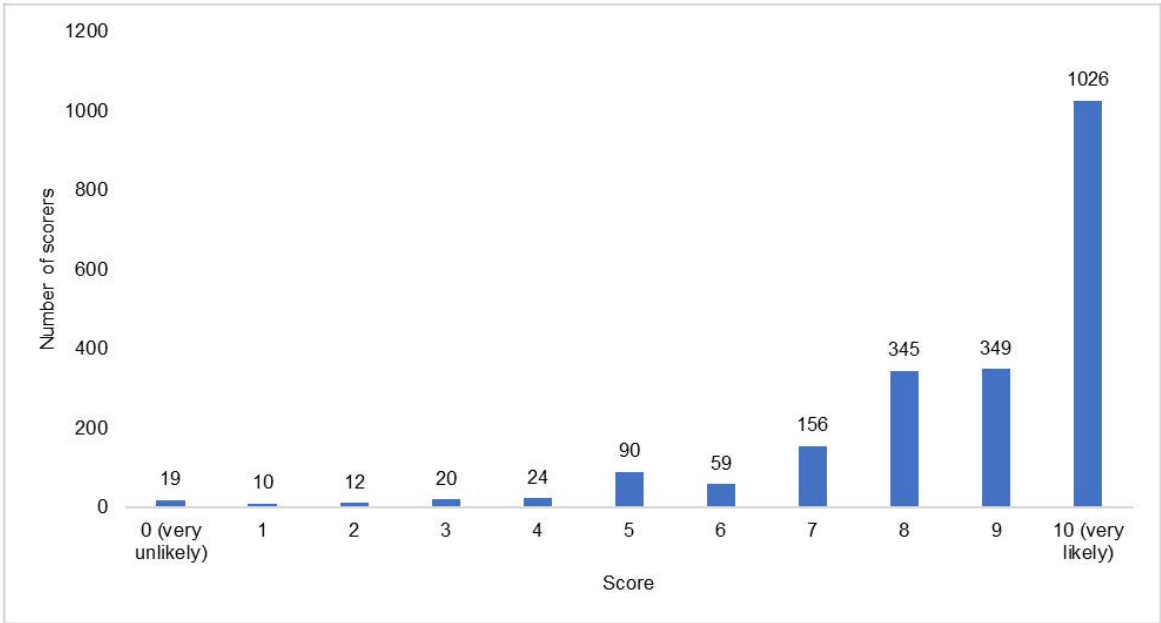

Figure 1. Frequency of user responses stating how likely they were to recommend Perx.

Why did you give this score?

Negative Responses

The most frequent negative responses were related to reward frequency (n=101) (Table 1) where user comments included *"The rewards aren't given that easily I feel like you go months before you win something."* The next most frequent responses came from users that had

experienced an overall negative encounter whilst using the application (n=55) (Table 1) stating *"...it can be a chore at times*." Other frequent negative responses included *"different gift vouchers"* when patients commented on the types of rewards offered by Perx (n=50) (Table 1), *"Still a few bugs to iron out"* when patients discussed technology issues (n=47) (Figure 2) and *"The facts...there's way too much repetition"* when patients described the repetitiveness of fun facts (n=43) (Table 1).

Positive Responses

The most frequent positive responses were from users that had an overall positive experience whilst using the app (n=569) with examples stating *"... Because it's a great app for everyone young or old."* This was followed by responses stating that Perx increased user medication adherence (n=344) (Table 1). *"Before my medication [adherence] was very adhoc. Yes, take it or not. Now [I'm] excited [to take my medication]. I tell people go on computer and inquire [about Perx]. Now I take my medication on time. Thankyou."* Other frequent positive responses included when patients commented on the reminder component of Perx (n=276).*"I love this app and couldn't endorse it enough. This app reminds me to take my medication when I usually wouldn't," "Great app love winning prizes for taking my medication"* when patients discussed the inclusion of rewards (n=184) and *"It's great to motivate and keep me on track"* when users described that Perx was motivating (n=116) (Table 1).

Themes and Categories		Responses, n[a]	Themes and Categories		Responses, n[a]
Positive		569	**Negative**		55
1.	**Behavioural**	1	**1.**	**Behavioural**	**3**
i.	Community	1	i.	Community	1
ii.	Compliance	344	ii.	Compliance	32
iii.	Motivation	116	iii.	Motivation	11
iv.	Condition Management	3	iv.	Condition Management	4
2.	**Functionality**	2	**2.**	**Functionality**	**29**
i.	Dosage Setting	0	i.	Dosage Setting	26
ii.	Ease of use	81	ii.	Ease of use	14
iii.	Glitches	0	iii.	Glitches	38
iv.	Medication List	0	iv.	Medication List	8
v.	Photos	0	v.	Photos	24

vi.	Sign In	0	vi.	Sign In	7
vii.	Technology	4	vii.	Technology	47
3.	**Components**		**3.**	**Components**	
i.	**Fun Facts**	2	**i.**	**Fun Facts**	5
a)	Content	2	a)	Content	13
b)	Repetitive or Frequency	0	b)	Repetitive or Frequency	43
ii.	**Games**	8	**ii.**	**Games**	8
a)	Frequency or Skipping	0	a)	Frequency or Skipping	16
b)	Type	10	b)	Type	28
iii.	**Reminder**	276	**iii.**	**Reminder**	26
iv.	**Rewards**	184	**iv.**	**Rewards**	25
a)	Frequency	7	a)	Frequency	101
b)	Type	83	b)	Type	50

[a]Categories may not add up to themes as responses could be coded into an overarching theme if they did not specify a category

Table 1. Frequency of positive (left) and negative (right) user responses stating why they assigned a particular score for Perx recommendation.

What is the one thing we could improve within the app?

The biggest area requiring improvement identified by patients was the rewards offered (n=322) (Table 2) where users stated, *"rewards and prizes."* Following this, responses indicated that nothing required improvement (n=178) by commenting such as *"Keep doing what you're doing it's great"* or *"I love it just as it is!"* when users had an overall positive experience while using the app (n=149). Other areas identified as requiring improvement include the games (n=125) where users commented *"developing some new games"* and *"keeping the app up to date so there is no technical issues"* when users described technology functionality (n=114) as needing improvement and *"update the facts/tips..."* when content of fun facts (n=114) required improvement. Finally, more personalisation of dosage reminders (n=96) was often mentioned with users stating things like "*personalising medication routines – I.e. days of the week, not just daily, every three days etc."* (Table 2).

Themes and Categories	**Responses, n[a]**

1. Positive	**149**
2. Nothing	**178**
3. Behavioural	
ii. Community	4
iii. Compliance	61
iv. Feedback	7
v. Motivation	26
vi. Condition Management	21
4. Functionality	
ii. Dosage Settings	96
iii. Ease of Use	35
iv. Glitches	68
v. Medication List	19
vi. Sign in	3
vii. Technology	114
viii. Photos	44
5. Components	
ii. Fun Facts	**258**
a. Content	114
b. Repetitive or Frequency	31
iii. Games	**125**
a. Frequency or Skipping	11
b. Type of Games	70
iv. Reminders	**77**
v. Rewards	**322**
a. Frequency	83
b. Type	95

[a]Categories may not add up to themes as responses could be coded into an overarching theme if they did not specify a category

Table 2. Frequency of user responses stating what improvements are required within the application.

Discussion

Analysis of responses from users receiving an mHealth medication adherence intervention demonstrated overall user acceptance towards the app. This acceptance can encourage patient

engagement assisting to establish the idea that using a mHealth intervention utilising gamification concepts and rewards is a feasible strategy to improve medication adherence.

Reminders, a technical component, are a common feature used in mHealth and have been extensively used in research aiming to improve medication adherence.[9] Previous research has examined patient perceptions on reminders within mHealth interventions stating that they are generally well accepted amongst patients as long as they are not too frequent.[17] This supports the trend in the results where Perx users appreciate the use of reminders within the app and found them to be helpful for being adherent. Reminders have repeatedly been a successful intervention component in improving adherence and their acceptance has most likely been crucial in their success.[9] However, their effectiveness is only sustained over time when in combination with other components and may be due to reminders targeting only one barrier to adherence, forgetfulness. There still can be a negative effect seen when reminders are too frequent and overwhelming in a user's schedule.[11, 18] They can be perceived as an annoyance and therefore rejected even when necessary. It is therefore vital to sparingly use reminders for only important actions that users perceive as necessary, such as when a medication dose is due.

Studies have confirmed that rewards can encourage patient perception changes by appealing to established theories of intrinsic motivation leading to increased patient engagement.[19, 20] Gamified systems such as mobile applications, commonly employ extrinsic motivational features such as: immediate success feedback through reward, continuous progress feedback and goal setting through reminders and support such as recognition, and comparison through leader boards or chat functions to provide emotional and value based rationales to influence patient engagement and in turn behaviour change.[20] All three of these main extrinsic motivational features (rewards, reminders and a social community) are utilised by Perx and two of them (rewards and reminders) were recurrent positive responses as to why users would recommend the application.

Although rewards were generally well accepted by Perx users, a recurring trend examined within the results was that low frequency of rewards was a precursor towards negative recommendation scores. A previous systematic review by Sardi et al. examined the role of rewards in providing feedback in eHealth applications.[21] The review stated that providing instant

feedback, such as rewarding gold points through gamification, was perceived by mHealth app users as a helpful mechanism by informing users about their current progress and alerting them to required changes in their health status.[21] Perx utilises a combination of instant and accumulated feedback processes. Instant feedback is offered in the form of pop-ups and visuals and accumulated feedback is offered in an "insights" tab to view an individual's previous adherence history on a visual graph.

It is important to note, that another frequent response was that patients perceived improved adherence from using Perx. Users' may only alone be perceiving improved adherence or they may be objectively viewing their adherence history within the app's insights feature. Moreover, our previous analysis of the Perx mHealth app concluded average high rates of adherence to medications and sustained adherence over six months, validating users' perceptions that their adherence was improved.[14] Feedback and review on progress, both within adherence and clinical outcomes, is a vital theme in allowing user satisfaction and continuing motivation. It is predicted that positive feedback, such as seeing a successful past history of being adherent, can additionally increase feelings of autonomy and competence.[22] Motivation is then created through an increase in need satisfaction. The positive perceptions of succeeding can continue to incite intrinsic motivation and in turn increased Perx patient engagement coinciding with improved medication adherence. This was additionally a common strength mentioned by patients in a recent review of mHealth perceptions. Patients highlighted the benefit of increasing patient empowerment with mHealth strategies' ability to facilitate self-management and create greater control and autonomy for a patient.[11]

Education in combination with other components has been found to be an effective intervention in improving medication adherence.[9] However, several barriers amongst health care practitioners delivering patient education have been identified.[23] Practitioner responses contributed to the general consensus that patients would not be interested in receiving educational materials.[23] Contrarily, Perx user perceptions showed that many users wanted additional daily educational materials to support their medication taking. Although the desire for educational materials was reflected within the results of this study, repetition of those materials was not. Repetition has been established as a cause of disengagement in previous literature.[19, 24, 25] The results of this study agree with this notion as one of the main negative

responses observed affecting user referral was repetitive fun facts. Several users reported that the information given through this component was not new and did not provide adequate support or information in helping improve their adherence or manage their condition. Although the educational facts were identified as the main tiresome component within Perx, reward type and games were also repetitive and in turn an area requiring improvement and barrier towards app recommendation via user responses. By introducing new and innovative medical facts, games and rewards, patient engagement, and in turn satisfaction will increase leading to a potential improvement in medication adherence. Adding to the utilisation of gamification concepts within the Perx mHealth app, educational games have been proven to be successful in the classroom and this would be expected to translate into adult health education as well.[26, 27] As long as the material is updated and non-repetitive for users, quizzes focusing on information about medication and disease states could be a potential new and exciting delivery form of education for users.

A major theme seen previously in literature surrounding patient perceptions of mHealth was tailoring of the intervention and the need for greater personalisation.[11] Some examples highlighted were patients being able to press a "snooze" button if the medication could not be taken right away. It is not surprising that Perx users responded the same, with 96 responses wishing dosage settings could be tailored more. While medication schedules may seem rigid, the patients' lives in which they are implemented may not be. Tailored settings to allow for travel, weekend routine differences, or hospital visits were often requested. It is therefore recommended that the Perx mHealth app, as well as other health behaviour change apps, allow for greater personalisation of reminder and notification settings within the app.

MHealth interventions are in an advantageous position to allow greater personalisation and reaction to user requests. While typical previous interventions to improve medication adherence relied on a healthcare professional often limited by training in intervention delivery, mHealth strategies have an ability to easily and swiftly be adjusted and updated to reflect user feedback. Resources may still be required to adjust mHealth interventions, but they remain less resource- and time-intensive than traditional strategies such as healthcare professional-delivered education, motivational interviewing, or pillboxes. Due to the fast adaptability of these approaches, mHealth may allow greater and quicker improvement in patient health outcomes.[1]

This implies that mHealth interventions should continue to be explored more frequently in their effectiveness on patient health outcomes and should be seriously considered as a recommended intervention avenue to incite behaviour change.

With a large amount of qualitative data, in-depth analysis is not always feasible. Modern methods of text mining and machine learning should be explored and utilised for a more efficient process to understanding users' experiences. Advanced methods of machine learning can also use these responses to personalize approaches and integrate more preferred components for the users that find them most helpful."

While proving that Perx was widely accepted amongst its users, there were some limitations in the study. First, multiple responses were seen per user thus responses could change over the time they use the app. This could make gauging a decisive positive or negative view of the application difficult. This was accounted for by averaging scores of first last response of users, with the average score remaining relatively the same (8.57 vs 8.54). Second, while two researchers undertook the data analysis with a small sample comparing results, moderator bias could still be present. Last, survey answers were only provided by users prompted to answer after one week of using the app or users willing to take the time to enter a response. Other users, such as those using the app for less than a week or those unwilling, would not be included in the analysis, eliminating a key population in those not engaging with the app.

Future research should aim to analyse health care professionals' opinions and perspectives on the Perx app to potentially gain their acceptance leading towards implementation into the health care system. A cost-effective reward frequency should also be determined to uncover the feasibility of long-term implementation of the application.

Conclusion

The use of a mHealth app utilising gamification and reward components to incite health behaviour change is an intervention that is widely accepted by its users. Most respondents would recommend using the intervention. Respondents enjoyed the app overall but especially reacted positively to reminder and reward components and stated that it improved their medication adherence, highlighting the desirability of these features in an mHealth app by users.

To improve the app, respondents would like higher reward frequency, functionality issues such as glitches to be eliminated and updated educational material. Further research should aim to analyse other stakeholders' perceptions of the mHealth app as well as its the cost-effectiveness to determine its long-term feasibility and implementation.

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Chapter 6

Discussion and conclusions

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Discussion

The overall aim of this thesis was to examine the effectiveness of interventions to enhance medication adherence across all disease states through a network meta-analysis, evaluate the effectiveness of an innovative mHealth intervention implemented, and explore the beliefs, perceptions and experiences of its users. The need for understanding the components for effective interventions at improving adherence was a theme observed across the body of work. There was an emphasis on the necessity for accurate description and evaluation of new mHealth or reward-based interventions' impact on adherence and their acceptability by the patients using them. The lack of research and guidance within the mHealth sector highlights a need for analysis of interventions implemented within consumer markets and a requirement in evaluating mHealth user beliefs and perspectives surrounding these interventions.

Medication non-adherence results from multiple factors and determinants within varying dimensions of the healthcare system, condition, treatment, socioeconomic context, and the patient. (Kardas, Lewek & Matyjaszczyk 2013) Multicomponent interventions aim to address multiple factors affecting the medication-taking process, resulted in effectiveness in improving adherence. (Nieuwlaat et al. 2014) This is a collective conclusion amongst the literature and was a main finding of our research in chapter 3 within our network meta-analysis assessing adherence interventions greater than 10 months. (Wiecek et al. 2019)

With an ability to incorporate multiple effective components, mHealth interventions are quickly gaining popularity as a supportive tool in assisting patients with all aspects of their healthcare. (Xiong et al. 2018) They have the potential to encompass several interacting components to facilitate the medication-taking process in a convenient method easily accessible to patients. (Silva et al. 2015) Evidence to support these rapidly developing mHealth interventions that aim to improve medication adherence is currently lacking, however, such research is vital to their successful implementation as

evidence-based health tools. Finally, understanding their acceptability by exploring the beliefs, perceptions and experiences of their users is essential for identifying their use, role in health care systems and long-term engagement. (Ahmed et al. 2018; Park et al. 2019)

Effective Interventions to Improve Medication Adherence

Our previous knowledge identified the most effective interventions at improving adherence to be multicomponent "package" interventions. (Nieuwlaat et al. 2014) The absence of understanding these effective interventions' working components identified a major gap in interpretation and replication of these successful strategies. Our network meta-analysis in chapter 3 allowed us to synthesise evidence from more than 400 studies on interventions aimed at enhancing adherence. We aimed to get a better understanding of what successful interventions are composed of and if certain combinations of components were more effective. We identified changes over multiple time periods for a better understanding of the evolution of adherence and interventions, as non-adherence is not a one-time issue but a continuous and often life-time challenge for patients on chronic medications. (Kardas, Lewek & Matyjaszczyk 2013) Due to the prevalence of chronic diseases and therefore the necessity of chronic medication, there is a focus on long-term adherence outcomes greater than 10 months and a need for interventions able to sustain long-term optimal adherence.

While a gold-standard intervention to improve adherence does not exist, we have discovered our results fit previous conclusions that multicomponent interventions are needed to enhance adherence over a long period of time (exceeding 10 months of duration). (Nieuwlaat et al. 2014) We can be confident from these results that one type of intervention, or a singular component intervention, will not be as effective alone in improving adherence long-term. Rather, components working together to target the

multiple dimensions of the medication-taking process are needed to sustain high levels of adherence across most populations. (Allemann et al. 2016; Kardas, Lewek & Matyjaszczyk 2013) Therefore, there is a need for the replication and feasibility of delivering these complex interventions within our health care systems.

While the network meta-analysis did not observe interventions across populations, a sub-analysis manuscript from our research team explored interventions with durations of 10 months or more and their effectiveness across disease states. Effectiveness of interventions did seem to relate to disease state, with educational and technical interventions being the most successful within patients with HIV infections and circulatory system and metabolic diseases, and attitudinal interventions showing a higher effect on musculoskeletal and mental, behavioural or neurodevelopmental disorders. (Torres-Robles et al. 2018) Conditional-related determinants of medication adherence can range from presence of symptoms, clinical improvement, disease severity, disease duration, and psychiatric conditions. From these numerous factors based on an individual's disease or co-morbidities, logic follows a conclusion that effective interventions would vary based on these conditions. A tailored, easily adaptable and multifaceted approach may be needed for individuals to understand their specific determinants with their condition or multiple conditions. (Allemann et al. 2016; Torres-Robles et al. 2018)

Patients will often have differing causes of non-adherence. (Ahmed et al. 2018) As discussed in the background, these different causes may require different interventions. The best approach may be for tailored interventions based on a patient's specific barriers and characteristics. Tailored interventions targeted at identifying patient barriers to adherence and offering solutions based on those barriers have tested in the past with modest effectiveness. (Grant et al. 2003; van der Laan et al. 2018) A trial on hypertensive patients used a nurse-delivered telephone intervention to assess patient barriers to adherence ranging from adverse effects to stress and literacy. While a 9%

increase was seen from baseline adherence rates, the extensiveness of the strategies offered combined with the necessary training of nurses to deliver the intervention create difficultly in the ability to replicate the intervention and results. (Bosworth et al. 2008) From other tailored interventions reported in the literature, a lack of describing intervention components make it difficult to replicate and offers a challenging approach to examine and understand their effectiveness. (Grant et al. 2003) A starting point in comparing effectiveness of these interventions may be through determining an agreement on ways to describe components of interventions delivered. While guidelines have been proposed, there is no consensus on a preferred method with literature not often utilising any guidelines. (Agarwal et al. 2016) Additional detailed protocols may also be a helpful tool in training those delivering tailored interventions, but consensus on strategies employed must be reached.

Within our network meta-analysis in chapter 3, technical intervention components (those aimed at simplifying or facilitating the medication taking process) were commonly utilised and highly effective. The most common types of technical interventions included reminders, simplification of drug regimen, medication aids, and monitoring and feedback of adherence. Reminders have been established as a desirable intervention though they are thought to be only effective on patients with nonintentional reasons for adherence, such as forgetfulness. (Tao et al. 2015) Nevertheless, technical components including reminders were consistently seen to be highly effective in our network meta-analysis and were ranked as the most effective intervention when combined with rewards in long term follow-ups greater than 10 months.

From the systematic review of mHealth apps effectiveness discussed in chapter 1, all twelve studies included in the review featured a reminder component within the app. (Leite et al. 2010) These were often dosage reminders but were widely found to be effective in a mobile phone avenue and desirable. (Kosse et al. 2019a; Mohan et al. 2018) Additionally, they appear to be more effective when combined with other components

such as education or behavioural type interventions, seen within our network meta-analysis. (Wiecek et al. 2019) While speculated that the effectiveness of reminders may diminish over time, technical components including reminders within chapter 3 were seen as the most effective in long term follow-ups greater than 10 months. (Tao et al. 2015) Longer duration studies over 24 months may be needed to understand the lasting ability of reminders on adherence. Finally, a surprising characteristic of reminders that may not be as important as one would assume is frequency. Significant differences have not been seen from frequency of reminders, ranging from multiple reminders per day to one per week; however, reminder fatigue should still be a consideration. (Tao et al. 2015) While not extensively researched within patients, "reminder fatigue," or the overuse of reminders may result in reminders being ignored. (Backman et al. 2017)

Rewards-based Interventions

Through our network meta-analysis, technical in combination with reward components (those creating incentives to be adherent) were often seen across time as the most effective intervention combination. Substantial effects were seen on adherence in short term studies less than 3 months, and long-term research over 10 months. The difficulty with basing conclusions from these results derive from the fact that the quantity of studies evaluating these intervention types, specifically reward-based interventions, was limited (n=7) compared to other interventions including educational or attitudinal components. Even considering the limited amount of research, the notable results warrant a more in-depth exploration of rewards, particularly in combination with other components, as a method of improving adherence.

The seven studies with interventions including a reward component included cash given to patients for being adherent and a decrease of drug co-payments. Acting as positive reinforcers, or a reinforcing desirable stimulus as a consequence aimed to repeat favourable behaviour, rewards have high potential to incite positive health behaviour

change. (Giles et al. 2014; Lattal 1991) In most studies, rewards were often monetary incentives of low value less than $5-$10 at a time,. (Malotte, Rhodes & Mais 1998) Interestingly, lottery-based incentives seemed to have a similar effect on improving adherence with any amount. A daily expected value of $3 was as successful as a daily expected value of $5. (Volpp et al. 2008) Recent research has also looked into lottery incentives for adherence, suggesting that lottery size, or the amount of value or chance of winning, may not have a substantial effect on adherence overall.

Additionally, participants seemed to remain engaged after 6 months of a lottery program, suggesting lottery-based interventions have the potential to continue to engage patients and improve adherence long-term. (Humphrey et al. 2019) Through the effectiveness of lotteries, it seems that regret messaging within these interventions plays a large role in patient psychology and effectiveness. Regret theory states that perception of loss is greater than the enjoyment of winning, or in simpler terms, we hate to lose more than we love to win. (Loomes & Sugden 1982) This theory seems to hold true within the fact that lotteries can be an effective approach to enhancing medication adherence. (Kullgren et al. 2017)

Through behavioural economics we understand that humans are often irrational and do not always correctly value rewards. (Earl 1990) Humans generally tend to have excessive optimism about receiving a positive outcome such as a lottery win even when the value purchase price of that lottery ticket in relation to the chance of winning indicates a loss in value. (Sharot 2011) Lottery-based interventions to improve adherence should be furthered explored not only on their effectiveness but also on how users perceive them, in addition to the feasibility, implementation with health systems and their cost-effectiveness.

The Perx intervention aims to employ lottery incentives within their rewards by using random rewards versus expected. The lottery creates regret theory by the user believing

not taking their medication dose results in a loss and by the user believing they may have won a reward had they taken it. (Loomes & Sugden 1982) Perx users may therefore be more likely to feel intense regret by missing medication doses and would try hard to avoid this feeling of loss, that is perceived as stronger compared to a feeling of winning. This strategy may create lasting engagement, as we saw in our analysis in chapter 4, as users had consistently high adherence rates above 80% over the full 6 months. Additionally, this is known in psychology as variable ratio partial reinforcement schedule. Most commonly seen within gambling, a variable ratio delivers positive reinforcement after an unpredictable number of responses to produce a high and steady response rate. (Lattal 1991)

We must not dismiss ethical concerns with lottery-based or incentive-based interventions. Financial incentives are increasingly becoming more important within motivating health behaviour change, yet they still only remain a single strategy within a complex issue. Oftentimes these strategies can be seen as ethical in that they improve health outcomes and guide patients towards better health choices. (Vlaev et al. 2019) Negatively, monetary compensation can also mute intrinsic motivation, meaning a patient may feel less inclined in the future to perform a positive health behaviour, such as taking their medication on time, without a reward. Others may see incentives as a form of bribery or coercion that may take advantage of certain types of populations.

Following this, research has consistently observed that individuals do not always act according to their long-term interests, such as improving their health. We often discern that patients regret decisions in their past, such as eating unhealthy food or smoking, yet their behaviours do not reflect their intentions. (Vlaev et al. 2019) While we may argue the ethics of rewards, they are assisting patients in adjusting their actions to their long-term preferences, such as healthier behaviour. (Marteau, Ashcroft & Oliver 2009) Financial incentives have long been commonplace within public policy and private organisations and seem to be increasing in frequency rather than decreasing. Small

evidence additionally shows that the public supports incentive schemes as long as they are cost-effective, and the majority do not interpret them as coercion. (Giles et al. 2015; Wadge, Bicknell & Vlaev 2015)

Furthermore, there is lacking data on the feasibility of implementing these financial incentives on a large scale within health. Limited research has proven cost-effectiveness in similar health incentive interventions, yet future research will need to examine more closely cost-effective analyses within different contexts as well as implementation and sustainability of these strategies into health care systems. (Crespo-Gonzalez, Garcia-Cardenas & Benrimoj 2017; Lee et al. 2019)

Incentives alone will often not be sufficient enough to change behaviour without additional context. Incentives may be used as a motivator but can often fade on their value over time. (Gneezy, Meier & Rey-Biel 2011) Behavioural economics has extensively researched and concluded that when you begin rewarding a behaviour, the reward for that behaviour will continue to be expected. (Ariely 2016) Therefore, when we reward patients with vouchers for taking their medication correctly and on time, the patients will continue to be expected for this behaviour for each dose thereafter. Within our qualitative assessment of Perx users, we found this trend in some users. While many users expressed their desire and the appeal for rewards within the app, others revealed anger and frustration at not receiving rewards frequently enough over time.

To combat this, as stated in chapter 4, Perx include multiple other components within their intervention. These include educational components, monitoring and feedback components (technical), supportive and motivational communication components (attitudinal) and gamification components (rewards). Gamification is the “application of game elements for purposes other than their expected use for entertainment.” (Dicheva et al. 2015) The Perx intervention utilises gamification concepts within by a “points” system in addition to daily streaks. These points and streaks within the app create a

similar sense of reward that a monetary incentive does in addition to habit forming a behaviour. (Mekler et al. 2013) Not only acting as an incentive, streaks can act as an additional dimension creating regret. If a patient does not take their daily dose and report within the app, their streak is over, rendering a consequence in loss of a greater reward. To avoid this regret and consequence, patients are more likely to be adherent. (Chou 2019)

Gamification concepts are limited in their research but have been studies within health behaviour change. They have been identified to often include the same techniques highlighted in the behaviour change techniques (BCT) taxonomy, an internationally recognised system of intervention components aimed to behaviour change. (Edwards et al. 2016) Within research, the BE FIT Randomised Clinical Trial game design significantly increased physical activity among families utilising the program. (Patel et al. 2017) Identifying similar behavioural economic theories in their game design, the Perx intervention created similar engagement and effectiveness over time seen in this previous research.

While rewards through the Perx intervention may be a motivating factor in being adherent, the additional context of the other components, including gamification concepts and technical components like reminders and feedback proven within research to improve health behaviours, may be necessary. Future research should evaluate more in-depth the components being used within the Perx interventions.

MHealth Intervention Content and Behaviour Change

Mhealth interventions delivered through apps create an innovative approach to managing medication adherence. The technology behind mobile apps allows quick changes and adaptability in delivery to users that may offer an easier avenue in tailoring adherence interventions to the individual patient. While hundreds of apps with this aim

remain on the consumer app stores, research is lacking on evaluation of intervention content. (Morrissey et al. 2016) Studies on effectiveness can help develop future recommendations on interventions to utilise, yet effectiveness outcomes can remain useless if the intervention is not fully understood to be replicated or implemented, or if they are poorly accepted by the patients using them. Examples of this were seen in the previously discussed tailored interventions. (Grant et al. 2003) These interventions were effective in improving adherence, yet the extensive training of staff delivering the intervention and unavailability of a transparent protocol prevent their replication.

Interventions, such as mHealth apps aimed at changing health behaviour, are increasingly complex with multiple components, as seen in the Perx intervention described in chapters 4 and 5. Specifically, within medication adherence, multicomponent interventions have been the most successful in improving adherence outcomes long term as we discovered in chapter 3. Due to these interventions requiring many parts and roles interacting together, they become difficult to replicate within research and challenging to implement within everyday healthcare practice. (Nieuwlaat et al. 2014) Additionally, complex interventions are often evaluated as a "package" without realisation of the most effective individual components. (Care 2009) While our network meta-analysis aimed to identify the most effective combinations of components, we were still limited by having to broadly categorise intervention components in order for a comparison. Moreover, poor description of interventions within research and protocols, in addition to published interventions using differently labels for similar strategies, create difficulties in duplication and uncertainty in understanding of why specific interventions, or their components, are effective. (Michie et al. 2013)

Behaviour change techniques (BCTs), previously mentioned earlier in this discussion, are replicable components of behaviour change interventions or so called "active ingredients". To further identify the make-up of successful interventions in improving

medication adherence, BCTs can help to better understand the mechanisms utilised for behaviour change interventions and to further inform on continued development of productive interventions. (Michie et al. 2013) BCTs can occur alone in singular component interventions or can be used within complex, multicomponent combinations through a variety of delivery avenues. Through this identification, effective interventions can be understood more thoroughly by the BCTs associated and included within the interventions. Past reviews have identified effective BCTs for interventions aimed at supporting smoking cessation, prevention of sexually transmitted infections, and strategies to improve healthy eating and exercise. (Albarracín et al. 2005; Michie et al. 2009; West et al. 2010)

Before exploring BCTs within medication adherence and mHealth research, we must first define and understand these techniques and theories behind them. A recent taxonomy highlighted 93 distinct BCTs within 16 categories developed by a Delphi panel of behaviour change experts. (Michie et al. 2013) These 16 clusters include: goals and planning, feedback and monitoring, social support, shaping knowledge, natural consequences, comparison of behaviour, associations, repetition and substitution, comparison of outcomes, reward and threat, regulation, antecedents, identity, scheduled consequences, self-belief, and covert learning. (Michie et al. 2013) Specific techniques within these clusters have clear definitions and examples in order to be replicated.

Due to the complex, multicomponent nature of successful interventions in improving medication adherence, BCTs can be advantageous in defining, understanding, and replicating effective mHealth interventions. A recent content analysis used the BCT taxonomy to review consumer available mHealth apps aimed at improving medication adherence to understand the presence or absence of behaviour change techniques. (Morrissey et al. 2016) Of apps available, 166 adherence apps were identified and coded with BCTs found to be present. A total of only 12 out of the possible 96 BCTs were

identified within these. The most common were “action planning” and “prompt/cues,” found in 96% of apps, correlating with the most often utilised adherence component of reminders or alert notifications. “Self-monitoring of behaviour” and “feedback on behaviour” were also commonly identified. (Morrissey et al. 2016) Self-monitoring and feedback on adherence have been used across multiple interventions avenues including healthcare professional delivered or electronic, for the past decade. They have often been found to be effective in improving adherence and were found by a review by Demonceau et al to be the most common component included in the most effective interventions to improve adherence. (Demonceau et al. 2013)

Agreeing with the finding of BCTs within smoking cessation and weight loss interventions, BCTs used in apps aimed at improving medication adherence were limited. While the revelation of an absence of BCTs can be disappointing in replicating mHealth adherence interventions, it also offers an opportunity for insight and utilisation of theory when developing or improving apps for effectiveness and quality. (Morrissey et al. 2016)

Previously mentioned within this discussion, gamification concepts often correlate closely to behaviour change techniques. Specifically, gamification apps aimed at promoting health behaviour change included an average of 14 BCTs per app, identified in a review of 64 consumer available gamification-based mHealth apps. (Edwards et al. 2016) The inclusion of game concepts within mHealth approaches may create additional BCTs utilised within these interventions.

Future research should focus on not only including BCTs and theory when developing mHealth interventions to improve adherence, but to also explore and evaluate which BCTS or combinations of BCTs within apps are most effective at achieving the goal of sustained adherence. Before this can be achieved, theory-based apps will need to be identified as well as their measurable effectiveness in improving medication adherence.

Additionally, while theories may be informative in creating effectiveness in achieving outcomes, user experience of BCTs and their apps components must be evaluated through qualitative research.

The Perx Intervention

The Perx mHealth intervention was extensively described within chapters 4 and 5. However, identifying specific BCTs within the intervention can be exceedingly useful in understanding its success in sustaining adherence rates averaging at 87.6% over 6 months and its comparison to other effective mHealth interventions. Additionally, the Perx app was created based on theory, specifically from behavioural economic principles and gamification concepts, and its BCTs can be identified within the app.

First, the Perx intervention utilised common components and BCTs found within other mHealth apps such as prompts/cues (a reminder alarm), action planning (setting a reminder), self-monitoring (recording of a dose taken), and feedback on behaviour (graphical display of adherence). (Michie et al. 2013) Categorised as technical components, all of these individual strategies have been proven to be effective in improving medication adherence within past literature. (Demonceau et al. 2013; Sawyer 2002; Stawarz et al. 2016)

Uncommonly used components, such as anticipated regret (raising awareness of expectations of future regret about the unwanted behaviour) and material incentives and rewards for behaviour and outcomes set the Perx intervention apart from other medication adherence mHealth interventions. Within the 166 apps aimed at improving adherence in Morrissey et al. 2016, none included goal setting (of the behaviour, adherence), information about health consequences, anticipated regret, graded tasks (challenges to be adherence for a certain amount of doses), material incentives (anticipation of a reward for the behaviour, adherence), material rewards (rewarding

the behaviour), incentives (for the behaviour), reward (of the outcome, being adherent), or reduced reward frequency. (Morrissey et al. 2016)

While limited studies have tested rewards and incentives to improve medication adherence, we still found the few interventions including them to be highly effective in chapter 3 and have discussed why that might be earlier within this discussion. To the best of our knowledge, the Perx mHealth intervention is the first identified within the literature to deliver rewards and incentives through a mHealth method. Connecting with our findings from the network meta-analysis, the Perx intervention including a reward component was effective at maintaining optimal levels of adherence over 6 months.

These additional components and BCTs utilised within the Perx intervention may be part of its success seen in sustaining optimal adherence rates over 6 months and may be evidence that combining rewards with multiple other component strategies is effective at creating long-term engagement and efficacy. Future research should more closely evaluate the working components within the Perx intervention, the role in the engagement of users within the intervention and their correlating effect on different barriers to medication adherence.

User Perspectives on mHealth

Exploring user perspectives on mHealth interventions is crucial to understanding the patient-centred means of managing medication adherence through mobile phones. Considering their implementation through consumer stores such as Apple, Android, and Blackberry has skyrocketed in the past decade, perspectives are often missing from the main stakeholders themselves: the users. The acceptability of an mHealth intervention is fundamental for understanding the probability of adoption of the intervention among end-users and therefore its ability to have an impact on adherence across these

populations. (Agarwal et al. 2016) Within our content analysis of Perx users in chapter 5, we aimed to explore the beliefs, perceptions and experiences of users of the app in addition to gain insight into the interventions' acceptability, desirable components and areas for improvement.

A recent content analysis on 1323 user reviews available through Apple and Android app stores of 20 different apps targeting medication adherence were analysed. (Park et al. 2019) Three main themes emerged: (1) features and functions users appreciated; (2) negative user experiences; and (3) desirable features. The analysis found user reviews to be mostly positive and pointed out specific derisible features. Though it should be noted this correlated with the most common features available in the apps, such as reminders. (Park et al. 2019) Within the Perx intervention content analysis in chapter 5, a common theme was also desirable features, with reminders often cited as the most helpful followed by rewards.

Reminders have been identified as a useful tool for patients with unintentional non-adherence, though they are generally found to be more effective over time when in combination with other intervention components. (Wiecek et al. 2019) Multiple meta-analyses and systematic reviews have explored their effectiveness within experimental studies. Forgetfulness is an often-cited reason for medication non-adherence. (Gadkari & McHorney 2012; Lowry et al. 2005) Users experiencing forgetfulness are the most likely to find reminders useful and may be the reason why many users of mHealth apps and the Perx intervention desired the use of reminders and found them helpful in improving their adherence. (Kosse et al. 2019b)

Within the overview of user reviews of mHealth interventions, simple app designs and apps with user-friendliness were frequently appreciated. (Park et al. 2019) Often users will express frustration with difficulty navigating the app features or by having difficultly and too much time needed for inputting medications. While we found this theme

common within Perx users as well, they also requested more personalisation of dosage reminders necessary. A balance would be needed to allow for greater personalisation when required, but an ease to navigating this customisation. This need to greater personalisation is additionally found within app reviews. (Park et al. 2019) However, restrictions of reminders or creating reminders without WIFI is often a complaint as well as people having difficultly when their regimen includes multiple medications to input. Apps were also favoured if they included the ability to manage medications for multiple people and pets. (Park et al. 2019) While this was not a major theme within Perx users, we believe certain users, such as those caring for children on medications or elders on medication, could benefit from this ability and could be a future recommendation to improve mHealth apps. This personalisation of adjusting dosing schedules to be more tailored to an individual's schedule, or allowing flexibility for caregivers, could create higher acceptability and satisfaction within the Perx intervention.

Often found within reviews is that users commonly try and seek multiple apps before deciding on one that best first their needed. (Park et al. 2019) Over 800 apps will be offered by searching medication terms within app stores, making the selection of an app difficult and overwhelming. (Tabi et al. 2019) This suggests a need for new avenues of discovering apps, preferably high quality and evidence-based mHealth apps. Health care providers, specifically pharmacists, may be in the best position for assisting patients with identifying a beneficial app appropriate for the individual patient and their specific barriers to adherence. (Park et al. 2019) Research and evidence surrounded these mHealth interventions is necessary for healthcare professionals to be able to evaluate different mHealth options and to give an evidence-based recommendation based on a patient's needs.

Future Directions

While we have seen a successful intervention in sustaining high medication adherence rates across time, and one that is highly accepted and desirable by its users, future research is still required.

First, while our retrospective analysis of the impact on adherence rates had strengths in that it observed real-life environments of its users, the Perx intervention must be critically evaluated and optimal adherence rates confirmed within the gold standard of research – a randomised controlled trial. It must be explored to be effective across different populations including those vulnerable with inequal health outcomes and it must be also evaluated if it is similarly accepted by these populations. A randomised controlled trial within three clinical conditions has already begun within Australia and will conclude in 2020, informing of the intervention's effect in improving adherence outcomes as well as clinical outcomes.

Second, through this research we extensively tried to understand the innerworkings of interventions to explore why some are effective, why others are not, and if all components are necessary. MHealth apps offer an opportunity in their ability to collect large amounts of data by how users are using the intervention. Utilising data science techniques, evaluation of user pathways, user events and event attributes can offer invaluable insight into how the users are interacting with the Perx intervention and what routine the most successful cohorts are experiencing. This would assess user engagement within the app and determine the app's most useful components, through examination of medication reminders, clinical reminders, educational facts, gamification components or types of rewards claimed. These analytics would be further correlated to determine what Perx app components result in the greatest change in patient adherence rates and for optimisation of the intervention. (Levati et al. 2016)

Furthermore, machine learning and artificial intelligence (AI) are quickly developing fields of data analytics. These techniques of computer systems learning to perform specific tasks through inference rather than explicit instructions mean the collection of large amounts of data regarding components' effectiveness on differing barriers to adherence can be identified and analysed more efficiently by advanced computing techniques. A machine's ability to identify patterns and insights within data can surpass those of traditional statistical techniques and should be a future explored opportunity for health behaviour data.

We have understood that patients have different determinants and causes for non-adherence and that tailored interventions to these specific determinants, both within mHealth and outside, may be the most effective solution. Through understanding component use and its correlation to adherence, better insight into recommended and tailored approaches would be allowed while still being able to describe the barriers assessed and tailored approaches correlated. By using questionnaires to identify patient barriers to adherence, further exploration of cohorts of patients with common causes of non-adherence, such as those not motivated versus patients with forgetfulness, can advance the knowledge of specific components that are most effective for which cohort.

Finally, while we have explored user beliefs, perceptions and experiences with a mHealth intervention utilising reward and technical components, an evaluation of how such an intervention fits into the entire healthcare sector is recommended. An evaluation may focus on integrating the service into pharmacy and the wider health care sector, encouraging consumer engagement, and identifying barriers responsible for resistance of integration of the app and significant strategies to mitigate the resistance factors. Mixed methods anonymous survey and questionnaire designs to both users of the app and stakeholders such as healthcare professionals or caregivers, will allow insight into

implementation of the Perx intervention into the health care sector and barriers prohibiting its full sustainability.

Through a transdisciplinary approach for the utilisation of an innovative mHealth app to improve medication adherence, a full optimisation of the intervention itself and its implementation and sustainability into the health care sector is necessary. Critical insight and expertise from all multiple disciplines is required for a holistic approach such as this.

Methodological Strengths and Limitations

This thesis investigated components within effective interventions to improve medication adherence and explored the use of an mHealth intervention utilising multiple components. Multiple methodologies were used to analyse, evaluate and determine effective interventions in improving adherence while additionally evaluating the opinions and perspectives of patients using one such intervention.

Within the literature surrounding interventions to improve medication adherence, modest improvements have been observed from numerous methods and strategies. To attain a more in-depth analysis of components within interventions found to be the most effective, a network meta-analysis was employed (chapter 3). This was an innovative method not used within adherence intervention research, outside of HIV research, (Kanters et al. 2017) and was aimed to broaden the understanding of the innerworkings of effective interventions. Network meta-analysis allows multiple comparisons of interventions to each other, rather than a common limitation of only being compared to standard care. This method allowed an analysis of ranking of intervention types and combination of components within interventions for a better understanding of the effectiveness of these tools. (Tonin et al. 2019) Limitations within the network included the classification of interventions and components. We originally attempted to categorise interventions and components into twelve categories that were more detailed and exact. This more detailed attempted created too many nodes within our networks, rendering it unable to be analysed. Additional methods like using BCTs within the network or previous categorisations in the literature would also create too many nodes and combinations that would prevent applicable results. Therefore, our four-category system was created for the purpose of broader categories and less combinations able to be compared effectively within the networks.

An additional element of subjectiveness remains in the categorisation of interventions and within often lacking descriptions of interventions trialled. We tried to reduce this limitation by having two individual researchers independently categorise interventions before discussing disputes. Due to the broad range of interventions utilised within the literature and the quality of intervention description reporting, we were still limited in our ability to accurately classify intervention types. Additionally, we chose to avoid restrictions on population inclusion criteria, such as disease state, in order to focus on specific type of interventions and their working components. While including multiple populations could be seen as a strength in the reach of our conclusions, we were limited in that certain intervention types were only researched within certain populations (i.e. reward + technical within drug-abuse populations).

A concern following the network meta-analysis was that while reward-type interventions revealed effectiveness in improving medication adherence, especially when combined with other components, a lack of analysis surrounding these interventions was present. We aimed to fill this gap with an analysis of adherence rates across users of a mHealth app, Perx, utilising rewards to motivate adherence in addition to other technical, educational and attitudinal components. M-DOT measurements allowed an objective method of measuring adherence across users of the intervention for a six-month period. However, M-DOT still required the user to open the app to record the dose, therefore not being able to accurately measure adherence unless a user was engaging with the app. While only retrospective data on app users was available, we were limited on evaluating the app's improvement on adherence without data on a control group or baseline adherence rates. Our retrospective data also had a strength in that we could observe the impact on adherence in real-life environments or normal practice without the influence of patients being aware they are being monitored and evaluated. Additionally, a small cohort of app users was available with a six-month period of using the app consistently over the time period, disallowing further evaluation across clinical conditions, age groups or medications used. However, even within this

small cohort we saw positive trends of optimal adherence being sustained over six months. There still remains a limitation in only evaluating retrospective observational data. A randomised controlled trial is recommended to complement the real-world evidence and further validate the app's causation of adherence rates.

Qualitative content analysis of user survey data allowed insight into user beliefs, perceptions and experiences of using the mHealth intervention. Content analysis revealed centralising themes surrounding their opinions of useful components within the app as well as their frustrations. Insight was gained on which components users find the most useful and correlating this with research analysing effectiveness of these components. The survey often presented multiple responses over many months (once per month per user) for a majority of users. However, our analysis revealed consistency in highly rating the intervention over time, with no decrease seen in the average rating score. A major limitation of our analysis, however, was that a user was not approached with the survey questionnaire unless they began using the app for multiple days. This excludes the opinions of a crucial population of those patients not ever engaged with the mHealth intervention. Future recent may be able to address this limitation by identifying cohorts that disengaged with the app less than a week after their first use of the app and targeting surveys to examine their beliefs and experiences.

Implications for policy, professional practice and research

The fast pace of industry allows for mHealth innovative creations to quickly hit markets. While this creativity should not be hampered, these interventions aiming to change health behaviours, such as medication adherence, must also be scrutinised and examined. The influence of these interventions cannot be understated on their impact on patients and evaluation of both mHealth's interventions' effectiveness on the relevant outcomes, in addition to perspectives of their stakeholders, should be required. Currently, Australia does not have guidelines on recommendations for evaluating mHealth or digital health tools. Due to this, the Evidence Standards Framework for Digital Health Technologies created by the National Institute for Health and Care Excellence (NICE) is recommended. Different recommendations on analysis needed is based on different tiers, or classifications, of digital health interventions. (NICE 2019)

Regarding professional practice implications, as mHealth interventions continue to grow and come into the forefront of patient care, healthcare professionals stand as a vital resource in guiding patients. Healthcare professionals should be educated on the type of mHealth interventions being offered to their patients and should be able to place recommendations based on an individual patient's needs. While we understand this is currently an overwhelming task for any healthcare professional to understand the seemingly infinite option of mHealth tools, mHealth interventions based on theory and tested within the NICE Evidence Standards Framework should be those first recommended. Easier comparison of app reliability and efficacy is necessary in order for healthcare professionals to have confidence in recommending digital tools for medication and healthcare management. Healthcare professionals confidence in mHealth tools will assist in improvements to healthcare professional workload and efficiency of patient-centred interventions.

Within the research sector, it is imperative that research agencies, such as universities, combine efforts with industry partners to develop and evaluate mHealth interventions. The majority of mHealth apps already being utilised by patients were created by industry, were not based in theory, and have not be evaluated publicly. The ability of the research sector to collect data and scrutinise these interventions on their content, effectiveness, stakeholder's perspectives, usability and implementation ability is crucial in the success of creating positive health behaviour changes, such as improved medication adherence. Furthermore, the collaboration of research and industry sectors may produce translational research by employing peer-reviewed results and applying them within industry to better promote effective mHealth solutions among larger populations.

Additionally, research surrounding interventions to improve medication adherence must focus on the content and components of these interventions in their evaluations. The vast amount of literature has provided sufficient knowledge concluding multicomponent interventions are effective in improving adherence yet lacks clarification of the specific content or combination of successful components. New methods through data mining or multifactorial approaches are needed in the assessment of these complex interventions to understand their effective components in addition to accurate and detailed description of interventions able to be replicated.

Opportunities for mHealth

The fast-paced creation and uptake of mHealth interventions across all healthcare dimensions offers endless opportunity in improving the lives of patients everywhere. The progress seen thus far from mHealth interventions within medication adherence gives hope for easily implementable and effective solutions to assist patients in medication management. In this thesis, we examined the effective components within interventions aimed at improving adherence and their application within mHealth avenues. Exploring the views of an mHealth intervention's users offered insight into their positive desirability seen and ability to be highly appreciated. We recommend continuing to innovate mHealth solutions within medication adherence, but to follow guidelines in their necessary evaluation, examination and acceptability as digital tools to assist in improving medication adherence as well as fully reporting and evaluating their working components.

Conclusions

- Medication adherence is most effectively improved long term by multicomponent interventions targeting multiple causes of non-adherence. A lack of research surrounding the use of reward components, alone or in combination with other components, warrants further investigation into their use.
- An mHealth intervention utilising multiple components including rewards (monetary vouchers and gamification), technical components (reminders and feedback), educational components, and attitudinal components (supportive communication) was an effective method of sustaining optimal adherence levels over six months.
- The mHealth intervention was highly accepted by its users, who found it helpful to improving their adherence. App features users appreciated the most included technical (dosage reminders and feedback) and rewards but barriers to app desirability remain in their ability to be personalised as well as their ease of use.
- Innovative mHealth solutions to improving medication adherence are encouraged to be developed, yet the examination of their effectiveness, acceptability and evaluation of their intervention components is necessary in recommending evidence-based digital tools.

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Appendices

A. Negligible Risk Ethics Approval

Dear Applicant

Project title: Analysis of retrospective medication adherence data

You have declared your research as Nil/Negligible Risk and that it DOES NOT include any of the following:

* Establishment of a register or databank for possible use in future research projects
* Collection, transfer and/or banking of human biospecimens
* Any significant alteration to routine care or health service provided to participants
* Interventions and therapies, including clinical and non-clinical trials, and innovations
* Targeted recruitment or analysis of data from any of the participant groups listed in Chapter 4 of the National Statement (or where any of these participants are likely to be significantly over-represented in the group being studied) including:
  - Women who are pregnant and the human fetus
  - Children and young people (under 18 years)
  - People in dependent or unequal relationships
  - People highly dependent on medical care who may be unable to give consent
  - People with a cognitive impairment, an intellectual disability, or a mental illness
  - People who may be involved in illegal activities (including those affected)
  - Aboriginal and Torres Strait Islander Peoples
* Collection, use or disclosure of personal information (except where expert opinion is being canvased with full disclosure, consent and identification for use in the public domain)
* Collection, use or disclosure of health information
* Collection, use or disclosure of sensitive information
* Covert observation, active concealment, or planned deception of participants
* Activity that potentially infringes the privacy or professional reputation of participants, providers or organisations (except where expert opinion is being canvased with full disclosure, consent and identification for use in the public domain)
* Potential for participants to experience harm (e.g. physical, psychological, social, economic and/or legal)
* Direct contact with UTS staff/students, patients, consumers or members of the public (except where expert opinion is being canvased with full disclosure, consent and identification for use in the public domain)
* Participants who have a pre-existing relationship with the researcher (except where expert opinion is being canvased with full disclosure, consent and

identification for use in the public domain)
* People unable to give free informed consent due to difficulties in understanding the Information Sheet or Consent Form
* People in other countries

PLEASE NOTE: If at any time, the scope of your research changes to include one or more of the above categories, you are immediately required to submit a new application.
To access the National Statement on Ethical Conduct in Human Research, visit the NHMRC webpage: https://www.nhmrc.gov.au/guidelines-publications/e72

Please keep a copy of your Declaration form on file to show you have considered the risks associated with your research. You should consider this your official letter of approval.
For tracking purposes, you have been provided with an ethics application number, which is UTS HREC ETH18-2312N.

I also refer you to the AVCC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

Instructions for saving the declaration form can be downloaded from: https://staff.uts.edu.au/howdoi/Pages/Researching/Research%20ethics%20and%20Integrity/Human%20research%20ethics/submit-my-human-research-ethics-application.aspx

To access this application, please follow the URLs below:
* if accessing within the UTS network: https://rm.uts.edu.au
* if accessing outside of UTS network: https://vpn.uts.edu.au, and click on ""RM6 - Production"" after logging in.

If you have any queries about this approval, please do not hesitate to contact your local research office or Research.Ethics@uts.edu.au.

Kind regards

UTS HREC Ethics Secretariat
C/- Research & Innovation Office
University of Technology Sydney

E: Research.Ethics@uts.edu.au
https://staff.uts.edu.au/topichub/Pages/Researching/Research%20Ethics%20and%20Integrity/Human%20research%20ethics/human-research-ethics.aspx
PO Box 123, BROADWAY NSW 2007
[Level 14, Building 1, Broadway Campus]

REF: Ethics 2 -Neg Risk approved (c)