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Digital interventions to improve adherence to maintenance medication in asthma

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ABSTRACT

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

To determine the effectiveness of digital adherence interventions for improving adherence to maintenance treatments in asthma.

BACKGROUND

Description of the condition

Asthma is the most common chronic lung condition worldwide, affecting 334 million adults and children globally (Global Asthma Report 2014); it accounts for an estimated 400,000 deaths each year (Soriano 2017). Asthma can cause shortness of breath, chest tightness, and cough and typically presents with wheezing. Many people with asthma experience intermittent worsening of their asthma symptoms, known as 'exacerbations', 'flare-ups', or 'attacks' (GINA 2016). Attacks can be triggered by common irritants and allergens such as pollution, tobacco smoke, pollen, and house dust mites (CDC 2016). Asthma is often incorrectly diagnosed - both overdiagnosed and underdiagnosed - worldwide (Aaron 2017; Looijmans-van den Akker 2016; Nolte 2006; van Schayck 2000); treatment remains suboptimal. Most asthma-related deaths occur in middle- and low-income countries. Poorly controlled asthma places a huge burden on individuals, their families, and society (WHO 2013).

Asthma treatment falls into two categories - maintenance preventive treatment for long-term control of symptoms and prevention of asthma attacks, and more immediate short-term relief for acute management of symptoms and attacks (BTS/SIGN 2016). This review focuses on maintenance preventive treatment. The mainstay of asthma maintenance treatment for all but the mildest cases consists of regular inhaled corticosteroids (ICSs) (Barnes 1993), which are also commonly referred to as 'preventer' or 'controller' medications (i.e. the intention is that they are used once or twice daily (depending on the preparation), even when the patient is

well, to maintain control over symptoms). ICSs, which are delivered directly to a patient's airways via an inhaler or a nebuliser, work by suppressing the multiple inflammatory cascades that are activated in the airways of a person with asthma. Inflammation leads to increased mucus production and airway constriction, which in turn contribute to the symptoms of asthma. Reduction in underlying inflammation through sustained use of an ICS can result in symptom improvement and reduced asthma-related morbidity and mortality (Barnes 2003; Barnes 2015). Commonly used ICSs include budesonide, beclomethasone, fluticasone (propionate and furoate), mometasone, and ciclesonide. These can be given alone or in combination with other maintenance asthma medications such as long-acting beta$_2$-agonists (LABAs), leukotriene receptor antagonists (LTRAs), long-acting muscarinic antagonists (LAMAs), theophylline, and slow-release beta$_2$-agonist tablets (BTS/SIGN 2016). LABAs are add-on therapies that are used only in combination with an ICS, in separate or combination inhalers. LABAs work by keeping the airways open and relaxing the muscles of the airways but do not treat any underlying inflammation. As such, LABAs should be used only with an ICS - never alone. Examples of LABAs include formoterol and salmeterol. LTRAs are usually considered as add-on therapies to ICS or ICS plus LABA, although evidence for use of LTRAs is based largely on studies in which LTRA was added to an ICS. LTRAs work by blocking the effects of cysteinyl leukotrienes in the airways - these leukotrienes are released during asthma attacks and cause bronchoconstriction. Addition of LTRA to an ICS may lead to improvements in asthma symptoms and lung function (Joos 2008). LTRAs are usually given orally as a tablet formulation; the most common example is montelukast. In adults with asthma who do not respond to ICS and LABA, LAMAs such as tiotropium may be considered as add-on treatment. Other alternative add-on maintenance options include theophyllines or slow-release beta$_2$-agonist tablets (for adults only), which may improve lung function and symptoms. In patients with a high steroid burden who continue to have frequent asthma attacks, symptoms, and impaired lung function, injectable maintenance treatment with monoclonal antibodies may be considered. Anti-immunoglobulin (Ig)E monoclonal antibody injections such as omalizumab bind to free circulating IgE, thus reducing free IgE levels. This is given as a subcutaneous injection every two to four weeks. Anti-interleukin-5 monoclonal antibody injections such as mepolizumab have been examined by researchers yet remain unlicensed for use in many countries (BTS/SIGN 2016).

Despite availability of medical treatment, adherence to ICSs is suboptimal, with patients needing to take treatment every day, regardless of whether they have symptoms (Barnes 2015; Lasmar 2009; Williams 2004). 'Adherence' is defined by the World Health Organization (WHO) as "the extent to which a person's behaviour (such as taking medication) corresponds with the agreed recommendations from a healthcare provider" (WHO 2003). Current adherence rates reported in the literature range from 0 to 100%, varying between and within individuals, but are estimated to average around 50% (McDonald 2002; Nieuwlaat 2014; WHO 2003). Adherence rates are estimated to be even lower in high-risk populations such as ethnic minority groups (Mathes 2014), as well as in developing countries (McQuaid 2012). Poor adherence to asthma maintenance treatment - in particular ICSs - is associated with increased morbidity and mortality. An estimated 383,000 asthma deaths have been reported worldwide (WHO 2013). In the UK, the National Review of Asthma Deaths found that 67% of asthma deaths were due to avoidable factors such as patients not taking their prescribed asthma medication in the month and/or year before their death (Royal College of Physicians 2014), highlighting non-adherence as a key modifiable determinant of mortality. Poor adherence is associated with considerable asthma-related morbidity: The risk of an asthma exacerbation is more than three times higher in patients after cessation of low-dose inhaled corticosteroids (Ebmeier 2017).

Investigators have identified several reasons for poor adherence, depending on the type of non-adherence. Broadly speaking, non-adherence can be classified as unintentional or intentional non-adherence. In unintentional non-adherence, patients do not adhere to prescribed treatment owing to factors not directly within their control, such as difficulties with medication-taking or access to treatment (Clifford 2008; Horne 2005; Kardas 2013). In intentional non-adherence, the patient makes a conscious decision to not take the medication; the patient chooses to not adhere owing to certain beliefs about treatment or perceptions of asthma (Clifford 2008), such as concerns around side effects of ICSs or lack of perceived personal need for treatment (Cooper 2015; Howell 2008; Menckeberg 2008; Ponieman 2009; Van Steenis 2014).

Description of the intervention

This review focuses on digital adherence interventions. No uniform definition of 'digital' can be found in the literature, and much overlap is evident between different classifications of digital interventions. In this review, 'digital' refers to interventions that are delivered via an online (web-based) platform (e.g. websites, web applications, online forums); a computer-based platform (e.g. mobile apps, short message service (SMS)-based interventions, games, interactive voice recognition systems (IVRSs)); or an electronic device of any type (e.g. electronic adherence monitoring devices). We will exclude from the review solely telephone-based interventions (e.g. health professional phone calls, telemonitoring, telehealth).

Online platforms

Online platforms, otherwise known as web-based platforms, include websites, web-based apps, and online forums; this term describes any intervention administered through a web browser online and requiring internet connectivity for delivery of the inter-

vention. These can be targeted to individuals or groups of individuals.

Computer-based platforms

This term describes any intervention that is delivered through computer-based platforms - such as via mobile, tablet, or desktop interfaces - and does not require internet connectivity for delivery of the intervention (Bussey-Smith 2007; Johnson 2016). These generally fall under the category of mobile applications, SMS-based interventions, or computer programmes or games.

Mobile apps

'Mobile apps' refer to software programmes designed for smartphones and tablets. Apps are optional add-ons to mobile devices that interact with users via a set of interfaces (e.g. a visual user interface). Asthma mobile apps usually aim to promote adherence by supporting overall asthma self-management skills, as through reminders or feedback on adherence (Marcano Belisario 2013). Apps can have many functions, including communication and collection of information from users and provision of interactive experiences. They provide a platform for delivery of adherence interventions that are considered to be highly customisable, of low cost, and easily accessible (Dayer 2013). However, challenges surround the use of mobile apps for delivery of adherence interventions. Engagement rates are often low, with few users downloading and using mobile apps on a regular and long-term basis, and concerns around privacy and data management remain (Anderson 2016; Krebs 2015).

SMS-based interventions

Most short message service (SMS)-based interventions aim to improve adherence by sending messages as reminders for medication-taking (Ali 2014; Kannisto 2014); with some interventions use SMS to deliver educational or behavioural messages to mobile phones (Tran 2014). The approach is usually low cost and may be customisable to address adherence barriers unique to each individual. A recent meta-analysis reported that use of SMS-based interventions to improve adherence could potentially double the odds of adherence across various chronic diseases (Thakkar 2016). The capability of SMS to relay information to many people without delay was cited by study authors as a key reason for exploring the potential of SMS-based interventions for adherence (Thakkar 2016).

Computer games or programmes

Computer games or programmes have been used increasingly as a method of intervention to drive changes in health behaviours (Johnson 2016). Interactive programme- or game-based interventions are postulated to be effective for influencing behaviour through their ability to motivate and stimulate engagement, particularly for children and adolescents. For asthma, game-based approaches have been used with some success to improve ICS adherence (Bussey-Smith 2007; Krishna 2003; Mosnaim 2015). These have ranged from simple games to educate and reinforce adherence behaviour (Mosnaim 2015), to complex interactive multimedia programs incorporating animation and scenarios of vignettes targeted to individuals or groups (Krishna 2003). However, difficulties with production and associated high costs are barriers that have limited their adoption and use in practice (Johnson 2016).

Interactive voice response systems

Interactive voice response (IVR) systems constitute a type of computer-linked telephone intervention system that uses several technologies to schedule, make, receive, or record automated phone calls, which can be used to promote adherence. IVR systems can be programmed to make and receive automated phone calls, ask questions, obtain feedback, and provide individualised information. Information can be tailored according to responses given through voice recognition or a touchtone keypad, and these systems have been used in several adherence interventions (Bender 2010; Reidel 2008).

Electronic monitoring devices

Electronic adherence monitoring devices (EMDs) have the ability to electronically record doses taken. EMDs can be used with different medication delivery devices including inhalation devices and pill bottles. Most EMDs measure, at minimum, the date and time of dosing, although more sophisticated devices are able to track the GPS location of doses, provide a customisable user interface, wirelessly transmit data to a linked mobile app, and provide dosing reminders (Chan 2013). EMDs can be used in adherence interventions as stand-alone devices or as part of a wider intervention. EMDs can track adherence patterns over time, and these can be shared with the patient and the healthcare provider via the device or through generated reports. Whilst EMDs can track the time and date of dosing, few can record inhalation or actual medication-taking. New devices such as the Inhaler Compliance Assessment (INCA) can record the sounds of inhalation (D'Arcy 2014); however the accuracy of this recording, whilst good, is still not perfect (Taylor 2018).

How the intervention might work

Digital interventions offer advantages in terms of adaptiveness, accessibility, reproducibility, and reach. Owing to the widespread use of digital technology, digital interventions can reach a large number of people, particularly in settings where access to either non-digital materials or face-to-face consultations is restricted (Masoli 2004). The ease of accessing digital technologies such as online

platforms, websites, and mobile phone apps may promote engagement with the adherence intervention (Baptist 2016; Dayer 2013). Digital interventions can also promote better communication between patients and healthcare providers (Dayer 2013; Eakin 2012). Digital interventions can support monitoring and recording of medication usage, asthma symptoms, or lung function, or all of these. Data can be fed back to patients in real time or communicated to their healthcare provider, thus facilitating a seamless transfer of health information across all interfaces of care (Chan 2013). This enables healthcare providers to gain access to detailed adherence information, which can provide insights into their patient's adherence behaviour that they may not otherwise have. This can add value to consultations by opening up conversations about adherence and drawing on actual, rather than assumed, adherence (Eakin 2012; Riekert 2002). Healthcare providers can be better equipped to provide recommendations personalised to the patient's behaviour. Patients can have the opportunity to reflect on the adherence data and their medication-taking behaviours, and to see how their adherence may be linked to their asthma control. For example, they may be able to identify patterns in their medication use that may be related to particular adherence barriers, allowing them to understand how this behaviour may be associated with their asthma symptoms.

Digital interventions also offer many interactive opportunities that non-digital interventions do not. This fact may enhance their effectiveness compared with non-digital interventions, which have limited interactivity and are primarily static, as patients may find digital media or interactive interfaces more engaging (Johnson 2016). Compared with traditional paper-based media, digital interventions can support the delivery of information in a variety of media formats that can be tailored to the patient's information preferences, thus increasing accessibility of the information in different populations (Baptist 2016). For example, users can choose how they want information to be presented to them, such as via a video animation or through text, and what kind of information they want. This ability to tailor can help target both unintentional non-adherence (e.g. through use of personalised reminders tailored to the individual's medication-taking routine (Britto 2012)) and intentional non-adherence (e.g. through use of messages sent to target and change negative beliefs or perceptions (Petrie 2012)). Digital technologies thus have the potential to deliver accurate information to patients in a timely manner, in a way that can be tailored to patients' healthcare needs and beliefs, and to provide practical medication support such as reminders and alarms. Besides improving engagement, use of different media can help increase the accessibility of health information for patients who may find traditional media (such as patient information leaflets) difficult to engage with - for example, patients with poor health literacy or visual or aural impairments, or those with learning disabilities such as dyslexia (Baptist 2016).

Digital intervention has been found to have issues that need to be considered before these methods are taken up and adopted into practice. These include concerns around data privacy, issues related to information governance such as accountability and liability around identification of non-adherence, ownership of adherence data, cost, impact on health disparities in terms of differences in ease of digital accessibility, and uncertainties around how best to incorporate digital interventions into existing workflow and health systems and how to train healthcare providers to respond to or use the collected information and how best to engage populations effectively (Anderson 2016; Krebs 2015; Michie 2017).

Why it is important to do this review

Medication non-adherence is one of the major health challenges facing modern medicine; poor medication adherence is associated with increased morbidity, mortality, and healthcare costs. In asthma, adherence to maintenance treatment such as ICS as the mainstay of treatment averages around 50%, although in some populations it can be as low as 20%, depending on the population and the method used to measure adherence (Sulaiman 2016; van Dulmen 2007; WHO 2003).

Poor adherence leads to significant morbidity in the form of poor asthma control, hospitalisations, days off work, and death (Suissa 2000; WHO 2003; Williams 2004). Many studies have highlighted the importance of good adherence in asthma - for example, Suissa et al found that the rate of death from asthma decreased by 21% for each additional canister of ICS used in the previous year (Suissa 2000); likewise Williams et al reported that every 25% increase in ICS use leads to 11% decreased risk of asthma exacerbations (Williams 2011).

In the UK, non-adherence to preventer treatment has been reported to be a factor contributing to approximately one-third of asthma deaths in one year (Levy 2014; Royal College of Physicians 2014). Interventions to improve adherence however have demonstrated limited effectiveness of adherence and assessment of outcomes (Nieuwlaat 2014). Part of the challenge of non-adherence is the difficulty involved in measuring adherence accurately and reliably. A range of methods are available to assess adherence directly (e.g. through direct observation of medication-taking or blood levels) or indirectly (e.g. via prescription or refill records, self-report, or electronic monitoring devices). However, all of these methods have their own advantages and disadvantages and can be subject to error (Farmer 1999).

Therefore it remains unclear how delivery of interventions can best support patient adherence to prescribed treatments. A shift within health care suggests that patients increasingly wish to take an active role in self-managing their own health and making their own healthcare decisions; this shift is driving the need for patients to be fully informed so they can make informed healthcare choices. Digital technologies, such as web and mobile platforms and electronic adherence devices, have been used increasingly as part of adherence interventions. Widespread use of smartphones and tablet computers provides a great opportunity for their use in delivery of

adherence interventions. Early evidence suggests that certain digital technologies - such as electronic reminder systems (Tran 2014) - may be effective in improving adherence, but questions remain around the size of this effect, and whether certain characteristics of digital interventions influence their effectiveness.

A recent Cochrane review focusing on interventions to improve adherence to ICS in asthma reported that adherence education, electronic trackers or reminders, and simplified regimens showed better adherence than controls (Normansell 2017). This review provided important information highlighting that electronic trackers or reminders may be effective in improving adherence. However, the review classification of 'electronic tracker or reminders' did not allow differentiation between the different types of digital interventions, and likewise, digital interventions (e.g. interactive voice recognition systems) were included under adherence education (Normansell 2017). More information is needed to determine whether certain types of digital interventions are more effective than others. The review was also restricted to only ICS as a medication class; to effectively answer the question around whether digital interventions can be effective for medication adherence behaviour in general, it would be useful to explore all classes of maintenance medication beyond ICSs. Adherence interventions also vary in terms of whether or not they are grounded in health psychology theory; recent evidence suggests that interventions that are behaviourally targeted and guided by theory may be more effective than those that are not (Conn 2017; Holmes 2014). Whether this applies to digital-based interventions remains unknown. Understanding whether use of theory is associated with more effective digital interventions is also important for this review - to inform future intervention development.

OBJECTIVES

To determine the effectiveness of digital adherence interventions for improving adherence to maintenance treatments in asthma.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) including cluster- and quasi-randomised trials. We will exclude cross-over trials and will include studies reported in full text, those published as abstract only, and unpublished data.

Types of participants

We will include both adults (aged 18 years and over) and children (under 18 years) with a diagnosis of asthma, as per international or national guidelines, or whose condition was diagnosed by a healthcare professional and are currently prescribed maintenance asthma treatment (via any administration route), given alone or in combination with other controller therapies. We will include interventions that target parents or carers who are involved in managing maintenance asthma medication for any participant. We will exclude interventions that are targeted at healthcare professionals, as the review relates only to digital interventions targeted at patients.

We will exclude participants with the following co-morbidities/characteristics.

1. Other respiratory comorbidities such as chronic obstructive pulmonary disease (COPD) or bronchiectasis.

We will include studies in which only a subset of participants meets the inclusion criteria (asthma diagnosis, prescribed maintenance treatment, or managing maintenance treatment for a participant diagnosed with asthma) if we can obtain disaggregated data.

Types of interventions

We will include studies comparing any interventions with a primary or secondary aim of improving adherence to maintenance asthma treatment (alone or in combination) that uses:

1. a digital component to deliver the intervention versus non-digital delivery of the same adherence intervention; or
2. a digital component to deliver an intervention versus usual care. Usual care is defined as standard asthma care as per evidence-based guidelines or standard care in the study setting.

Included digital interventions may be completely self-delivered or may include an 'in-person' or 'human' element whereby a healthcare professional or a trained peer is involved in the intervention. This can occur at the point of invitation to participate (e.g. introduction of the digital intervention and/or training of the patient to use the digital intervention) or on an ongoing basis (e.g. discussion of data from the digital intervention at regular consultations, use of remote adherence monitoring and feedback to the patient). The interventions may be delivered completely virtually (i.e. completely digital with no 'in-person' element) or may include some face-to-face aspect (i.e. has an 'in-person' element); delivery can be provided to individuals (e.g. with mobile apps or electronic monitoring) or to groups (e.g. online forums or computer games), and the intervention may be delivered on a one-off or ongoing basis.

We will include the following cointerventions, provided they are not part of the randomised treatment.

1. Cointerventions for which more than one type of digital media is used.
2. Other cointerventions that are used in asthma management

When interventions have been described in insufficient detail to determine how the digital intervention was used, we will contact

the authors of identified studies to obtain further information. In the case of non-response after initial contact, we will follow up with study authors twice (once every two weeks), if required. If we receive no response after three contacts, we will exclude these studies from the review.

Types of outcome measures

Primary outcomes

1. Adherence to maintenance medication as assessed by any objective or validated subjective measure of adherence
2. Asthma control as determined by any validated self-report instrument
3. Exacerbations requiring at least oral corticosteroid treatment (prescribed or taken - as measured by self-report or via objective measurement, e.g. from pharmacy dispensing or prescription records)

We have chosen these primary outcomes as these measures are the most likely outcomes to be used.

Secondary outcomes

1. Acceptability of the digital intervention (using any validated instrument or quantitative measure of acceptability such as dropout rates, proportion, of days on which tools were used, satisfaction with the intervention). We will exclude qualitative data or patient feedback.
2. Unscheduled healthcare utilisation (number of visits to a healthcare provider/attendance at an emergency department or urgent care centre/hospital admission (i.e. overnight stays))
3. Time off school, work, or other commitments due to asthma exacerbations or complications
4. Lung function as measured by peak expiratory flow rate (PEFR)
5. Quality of life as assessed by any validated standard instrument
6. Cost-effectiveness of the intervention (via any reported cost-effectiveness outcome such as impact on hospitalisation/ length of stay)
7. Adverse events

If outcomes are reported at multiple time points, we will extract these and will include the latest reported time point. We will exclude post-intervention follow-up data. If multiple measures of adherence are used, we will include the most objective measure in the review.

Reporting in the study of one or more of the outcomes listed here is not an inclusion criterion for this review.

Search methods for identification of studies

Electronic searches

We will seek assistance from the Cochrane Airways Information Specialist to identify studies from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group.

The Cochrane Airways Trials Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org).
2. Weekly searches of MEDLINE Ovid SP (1946 to date).
3. Weekly searches of Embase Ovid SP (1974 to date).
4. Monthly searches of PsycINFO Ovid SP (1967 to date).
5. Monthly searches of Cumulative Index to Nursing and Allied Health Literature (CINAHL) EBSCO (1937 to date).
6. Monthly searches of Allied and Complementary Medicine (AMED) EBSCO.
7. Handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. We will include details of these strategies, as well as a list of handsearched conference proceedings, in Appendix 1. See Appendix 2 for search terms used to identify studies for this review. These terms have been guided by previous Cochrane reviews such as the Normansell 2017 review (which identifies asthma adherence reviews, although we will not be restricting to inhaled corticosteroids) and the Marcano Belisario 2013 review (which focused on smartphone and tablet apps, although we will not be restricting the review to only these two digital media).

We will search the following trials registries.

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov).
2. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

We will search the reference lists of all primary studies and review articles for additional references.

We will search for studies from the year 2000, as technologies existing before this time are unlikely to be representative of contemporary technologies that support health apps - this is in line with the Cochrane smartphone app review by Marcano Belisario et al (Marcano Belisario 2013).

We will apply no language restrictions.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' websites for study information.

We will search for errata or retractions from included studies published in full text on PubMed and will report within the review the date this was done.

Data collection and analysis

Selection of studies

Two review authors (AC, ADS) will independently screen the titles and abstracts of the search results and will code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports of all potentially eligible studies, and two review authors (VW, CC) will independently screen them for inclusion, while recording the reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion, or, if required, we will consult a third person/review author (LH). We will identify and exclude duplicates and will collate multiple reports of the same study, so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We will use Rayyan (Ouzzani 2016) to screen titles and abstracts of identified studies based on the aforementioned inclusion criteria. We will then obtain full-text study reports/publications of included or potentially relevant studies, and two review authors will independently screen these to identify studies for inclusion and to identify and record reasons for exclusion of ineligible studies. We will resolve disagreements through discussion or, if not resolved, by consultation with the review team. We will exclude any duplicates and multiple reports of the same study.

We will use Covidence to extract study characteristics and outcome data. We will develop a data collection form to extract data and will pilot this form on at least one study in the review. Two review authors (from the following: AC, ADS, VW, LH, and CC) will extract the following study characteristics from included studies in duplicate.

1. Methods: date of study, study design and method of randomisation, length of follow-up, total study duration, details of any 'run-in' period, number of study centres and locations, study setting (healthcare setting and country), study withdrawals (study dropout and intervention dropout). We will attempt to distinguish between study versus intervention dropouts to better understand attrition behaviour, if possible, as per an earlier review (Sohanpal 2012)).
2. Participants: N (baseline and upon completion), mean age, age range, gender, severity of asthma, baseline lung function, smoking history, inclusion criteria, exclusion criteria, and differences between groups at baseline.
3. Interventions: intervention details, type of intervention (theory-based vs non-theory-based), details of intervention provider, intervention target (primary and secondary), types of digital components used (technologies used), number of digital components, number of intervention sessions, interactivity with patient (i.e. a two-way flow of information between the digital component and the patient), adherence feedback, concomitant medications, and excluded medications.
4. Comparison: details of comparison group.
5. Outcomes: primary and secondary outcomes specified and collected; methods of assessment of outcomes and time points reported.
6. Notes: funding of trial and notable conflicts of interest of trial authors.

Two review authors (from the following: AC, ADS, VW, LH, and CC) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person/review author (RH). One review author (AC) will transfer data into the Review Manager file (RevMan 2014). We will double-check that data are entered correctly by comparing data presented in the systematic review against study reports. A second review author (VW) will spot-check study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (from the following: AC, VW, ADS, and LH) will assess risk of bias independently for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another review author (CC). We will assess risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We will judge each potential source of bias as high, low, or unclear and will provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). When information on risk of bias relates to unpublished data or correspondence with a

trialist, we will note this in the 'Risk of bias' table.
When considering treatment effects, we will take into account the risk of bias for studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and will justify any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

For data reported as rates or times-to-events (e.g. exacerbations), we will analyse time-to-event or rate ratios. Reported rate ratios can be transformed into log-rate ratios and analysed via a random-effects model and by generic inverse variance (GIV).
We will analyse continuous data as standardised mean differences (SMDs) using a random-effects model and 95% confidence intervals (CIs). We will use mean differences (MDs) rather than SMDs however if measures are reported on the same scale, but we anticipate that most studies will use a variety of methods of measurement, in which case we will use the SMD. We will use the standard deviation (SD) of final (rather than baseline) measurements in the analysis. Although adherence can be presented as dichotomous or continuous, adherence generally is best considered as a continuous variable by nature (to avoid loss of valuable information and use of arbitrary cutoffs), which may be later dichotomised, depending on the adherence measurement method used (Saberi 2011). Therefore, we will treat adherence as continuous data in this review, and this will increase the power to detect a difference. We can adjust dichotomous data by applying a logit transformation and producing an SMD, which can be analysed via GIV. When available, we can use change from baseline scores.
We will undertake meta-analyses only when this is meaningful, that is, when treatments, participants, and the underlying clinical question are similar enough for pooling to make sense, for example, studies using a similar method of digital intervention. We will describe skewed data narratively (e.g. as medians and interquartile ranges for each group).
When a single study reports multiple trial arms, we will include only the relevant arms. If two comparisons (e.g. intervention A vs control and intervention B vs control) are combined in the same meta-analysis, we will combine the active arms or will halve the control group to avoid double-counting.
If adjusted analyses are available (ANCOVA), we will use these as a preference in our meta-analyses. If both changes from baseline and endpoint scores are available for continuous data, we will use change from baseline unless we note low correlation between measurements in individuals. In addition, we will not combine change from baseline and endpoint scores in analyses using the SMD. If a study reports outcomes at multiple time points, we will use the measure taken at the last follow-up. We will use the SDs of final (rather than baseline) measurements in the analysis.
We will use intention-to-treat (ITT) or 'full analysis set' analyses when they are reported (i.e. those in which data have been imputed for participants who were randomly assigned but did not complete the study) in preference to available case or per-protocol analyses, if both are reported.

Unit of analysis issues

For dichotomous outcomes, we will use participants, rather than events, as the unit of analysis (i.e. number of children admitted to hospital rather than number of admissions per child). However, if rate ratios are reported in a study (e.g. for exacerbations), we will analyse them on this basis. We will meta-analyse data from cluster-RCTs only if available data have been adjusted (or can be adjusted) to account for the clustering. In keeping with recommendations from the *Cochrane Handbook for Systemaitc Reviews of Interventions*, we will adjust cluster-randomised data by inflating standard errors using a design effect (DE) calculated with an intracluster correlation coefficient (ICC).

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study is identified as an abstract only). When this is not possible and the missing data are thought to introduce serious bias, we will exclude the study.

Assessment of heterogeneity

We will use the Chi^2 test of homogeneity and the I^2 statistic to measure heterogeneity among the studies included in each analysis. If we identify substantial heterogeneity, we will report this and will explore the possible causes by performing prespecified subgroup analysis. Higgins et al suggests using an I^2 value of 75% and over to indicate high heterogeneity (Higgins 2003).

Assessment of reporting biases

If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible small-study and publication biases using Egger's t-test.

Data synthesis

We will use a random-effects model and will perform a sensitivity analysis using a fixed-effect model.

'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes: adherence to maintenance medication; asthma control via any validated self-report instrument; exacerbations requiring at least oral corticosteroid treatment; acceptability of the digital intervention; unscheduled healthcare utilisation; time off school, work, or other commitments due to asthma exacerbations or complications; and any reported adverse events.

We will use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to studies that contribute data for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade the quality of studies by using footnotes, and we will make comments to aid the reader's understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Interventions that have used only one digital component versus interventions with multiple (more than one) digital component.
2. Different types of digital interventions (i.e. online vs computer-based vs electronic monitoring devices).
3. Interventions with an interactive component versus non-interactive interventions.
4. Digital interventions involving adherence feedback versus interventions that do not.
5. Theory-based versus non-theory-based digital interventions.
6. Interventions for ICS versus non-ICS therapies.
7. Primary versus secondary care setting (defined in terms of where participants were recruited for the study).
8. Interventions with an 'in-person' component versus interventions that are fully digital and self-delivered.

We will use the primary outcomes in the subgroup analyses.

1. Adherence to maintenance medication via any objective or validated subjective measure of adherence.
2. Asthma control via any validated self-report instrument.
3. Exacerbations requiring at least oral corticosteroid treatment.

We will use the formal test for subgroup interactions available in Review Manager (RevMan 2014).

Sensitivity analysis

We plan to carry out the following sensitivity analyses while removing these items from primary outcome analyses.

1. Unpublished data.
2. Trials with high risk of selection bias.
3. Trials via subjective adherence outcome measurement methods.
4. Quasi-randomised trials.
5. Non-English studies.
6. Commercially funded studies.

We will compare results from a fixed-effect model versus results from a random-effects model.

For cluster-randomised trials, we will run the main analyses using more and less conservative estimates of the ICC.

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The Background and Methods sections of this protocol are based on a standard template used by Cochrane Airways. The first background section of this protocol has been based on the published Cochrane review "Interventions to improve adherence to inhaled steroids for asthma" (Normansell 2017).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Trials Register

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify studies for the Cochrane Airways Trials Register

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.

8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11
The MEDLINE strategy and RCT filter are adapted to identify studies in other electronic databases.

Appendix 2. Search strategy to identify relevant studies from the Cochrane Airways Trials Register

#1	AST:MISC1
#2	MeSH DESCRIPTOR Asthma Explode All
#3	asthma*:ti,ab
#4	#1 or #2 or #3
#5	MESH DESCRIPTOR Web Browser
#6	MESH DESCRIPTOR Patient Portals
#7	MESH DESCRIPTOR Online Systems EXPLODE ALL
#8	MESH DESCRIPTOR Internet EXPLODE ALL
#9	(online* OR web* OR browser OR portal OR internet* OR virtual*):ti,ab,kw
#10	MESH DESCRIPTOR Cell Phones EXPLODE ALL
#11	MESH DESCRIPTOR MP3-Player
#12	MESH DESCRIPTOR Computer Systems EXPLODE ALL
#13	MESH DESCRIPTOR Mobile Applications
#14	((cell* or mobile*) near3 phone*):ti,ab,kw
#15	(handheld* or hand-held*):ti,ab,kw
#16	(smartphone* or smart-phone*):ti,ab,kw
#17	(personal* near3 digital*):ti,ab,kw
#18	(PDA OR "Palm OS" or "Palm Pre classic" OR blackberry OR nokia OR symbian OR INQ OR HTC OR sidekick OR android* OR iphone* OR ipod* OR ipad* OR samsung OR Huawei OR sony OR LG OR pixel OR (windows* near3 (mobile* or phone*)) OR (tablet near3 (device* or comput*))):ti,ab,kw
#19	(app* near3 (smartphone* or smart-phone or mobile* or phone* or tablet* or computer*)):ti,ab,kw

(*Continued*)

#20	MESH DESCRIPTOR Text Messaging
#21	(sms OR mms):ti,ab,kw
#22	((text* OR short*) NEAR3 messag*):ti,ab,kw
#23	texting:ti,ab,kw
#24	MESH DESCRIPTOR Reminder Systems EXPLODE ALL
#25	((electronic* OR medication*) NEAR3 (reminder* OR monitor* or record* OR system* OR device*)):ti,ab,kw
#26	(reminder NEAR3 (text* or system* or messag*)):ti,ab,kw
#27	alert*:ti,ab,kw
#28	wearable*:ti,ab,kw
#29	MESH DESCRIPTOR Speech Recognition Software EXPLODE ALL
#30	((interact* OR speech* OR voice* or touchtone) NEAR3 (recogni* OR respon*)):ti,ab,kw
#31	IVR:ti,ab,kw
#32	automat* NEAR3 (phone* or telephone* or call* OR system*):ti,ab,kw
#33	MESH DESCRIPTOR Communications Media EXPLODE ALL
#34	("social media" OR Facebook OR Twitter OR Instagram OR Snapchat OR YouTube OR WhatsApp):ti,ab,kw
#35	(video* OR television OR radio OR media* OR multimedia OR multi-media OR audio* OR webinar* OR podcast* OR wiki* OR interactive OR digital* OR tech*) :ti,ab.kw
#36	MESH DESCRIPTOR Telemedicine EXPLODE ALL
#37	MESH DESCRIPTOR Telenursing EXPLODE ALL
#38	(telehealth* or tele-health* or telecare* or tele-care*):ti,ab,kw
#39	(mhealth or m-health or "m health" or "mobile health"):ti,ab,kw
#40	(e-health or ehealth or "e health"):ti,ab,kw
#41	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
#42	#41 AND #4

(*Continued*)

#43	INREGISTER
#44	#43 AND #42

CONTRIBUTIONS OF AUTHORS

Chan A: draft the protocol; develop and run search strategy; obtain copies of studies; select which studies to include; extract data from studies, enter data into RevMan; carry out and interpret analysis; draft final review; update review.

De Simoni A: draft the protocol; develop and run search strategy; obtain copies of studies; select which studies to include; extract data from studies; enter data into RevMan; carry out and interpret analysis; draft final review.

Wileman V: draft the protocol; develop and run search strategy; obtain copies of studies; select which studies to include; extract data from studies; enter data into RevMan; carry out and interpret analysis; draft final review.

Holliday L: draft the protocol; develop and run search strategy; obtain copies of studies; select which studies to include; extract data from studies; enter data into RevMan; carry out and interpret analysis; draft final review.

Chisari C: draft the protocol; develop and run search strategy; obtain copies of studies; select which studies to include; extract data from studies; enter data into RevMan; draft final review.

Newby C: draft the protocol; carry out and interpret analysis; draft final review.

Fleming L: review the protocol; review final review.

Taylor SJC: review the protocol; review final review.

Griffiths C: review the protocol; review final review.

Horne R: review the protocol; review final review; update review.

DECLARATIONS OF INTEREST

Chan A: Amy Chan has received consultancy fees from Janssen-Cilag, speaker fees from Novartis, and travel grants from Maurice Phyllis Paykel Trust and Max Health for activities outside this submitted work. Amy is also a freelance consultant for the UCL-Business spin-out Spoonful of Sugar Limited.

De Simoni A: none.

Wileman V: none.

Holliday L: none.

Chisari C: none.

Newby C: none.

Fleming L: consultancy fees from Vectura, advisory board fees from Boehringer Ingleheim and Novartis: paid to my Institution; personal speakers fees from Novartis and AstraZeneca.

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