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Effect of monitoring adherence to regular inhaled corticosteroid (ICS) alone or in combination with a long-acting β2-agonist (LABA) using electronic methods on asthma outcomes: a narrative systematic review

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ABSTRACT

Objectives To evaluate through a systematic review the effectiveness of electronic methods in monitoring adherence to regular inhaled corticosteroids (ICS) alone or in combination with long-acting β2-agonists (LABAs) and their effect on clinical outcomes.

Design A narrative systematic review.

Data sources MEDLINE, EMBASE, Cochrane Database of Systematic Reviews and Web of Science were searched through up to 10 July 2022.

Eligibility criteria We included peer-reviewed studies of qualitative and quantitative outcomes that compared the effect of electronic methods to routine non-electronic monitoring intervention or placebo among children and adults with asthma on medication adherence rates to regular ICS alone or in combination with LABA, asthma control and asthma exacerbations.

Data extraction and synthesis Data extraction was performed according to a predetermined sheet specific to the review objectives. The risk of bias was assessed using the Cochrane Risk of Bias Tool for randomised controlled trials and the Risk of Bias in Systematic Reviews tool for systematic reviews. Meta-analysis was not possible based on the findings of the scoping search; however, a narrative review was performed to allow for the grouping of results based on asthma inhaler adherence rates, asthma control and exacerbations.

Results Six articles comprising 98 studies published from 1998 to 2022 in the USA, Canada and the UK were included. Compared with the control, electronic monitoring devices (EMDs) showed a 23% adherence improvement, mean difference (MD) of 23%, 95% CI 10.84 to 34.16, p=0.0002. Asthmatic children were 1.5 times more likely to be adherent using EMDs compared with non-EMD users (RR=1.5, 95% CI 1.19 to 1.9) (p<0.001). Mobile devices and text message reminders (MHealth) showed a 12% adherence improvement (MD 12%, 95% CI 6.22 to 18.03) (p<0.0001), alongside a small to medium improvement in asthma control (standardised mean difference (SMD) 0.31, 95% CI 0.17 to 0.44), small improvement in asthma-related quality of life (SMD 0.26) (p=0.007) and variable risk reduction in asthma exacerbations for digital health (risk ratio 0.53, 95% CI 0.32 to 0.91) (p=0.02) compared with EMDs, which showed insignificant differences (risk ratio 0.89, 95% CI 0.45 to 1.75) (p=0.72). Technologies combined yielded variable adherence effects, with an SMD for eHealth of 0.41, 95% CI 0.02 to 0.79, and MD for digital health was 14.66% higher than the control, 95% CI 7.74 to 21.57. Heterogeneity between studies was significant (eHealth I^2=98%, digital I^2=94%).

Conclusion Electronic methods improved adherence to inhaled medications in asthma. EMDs appear to be the most effective technology, followed by mHealth. The adherence improvement was associated with a small clinical improvement. There was inconsistent overlapping of terminology describing electronic methods that require standardisation. Data on the cost-effectiveness of electronic devices and their utilisation in severe asthma are lacking and require further research.

PROSPERO registration number CRD42022303069.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews.
⇒ Benefited from the multidisciplinary expertise of a lead in severe asthma service, pulmonologists and clinical pharmacists, evaluating and comparing the studies.
⇒ Used Cohen's d to compare different effect estimates of multiple studies that used various adherence assessment tools in monitoring adherence as an outcome since standardised mean difference alone tends to overestimate the effect size, especially with small sample size studies.
⇒ Not a meta-analysis.
⇒ Only two of the five identified systematic reviews were registered on PROSPERO, highlighting a need to avoid duplicating work through protocol registration.

BACKGROUND

Asthma is a common chronic disease characterised by chronic airway inflammation with a history of respiratory symptoms that vary over time. It is prevalent, affecting up to 18% of the population globally.[1]

Patient adherence to treatment is defined as using therapy as agreed with the healthcare professionals (HCP).[2] Uncontrolled asthma has significantly increased healthcare utilisation and costs.[3] The estimated unused medicines' cost in the National Health Service in the UK is around £100 million annually.[4] It has been estimated that 30%–50% of children and adults with asthma fail to use medications as directed.[5 6] Poor adherence to asthma medications can lead to asthma exacerbations, worse health outcomes, hospitalisations, higher mortality and increased healthcare utilisation. Non-adherence to regular inhaled corticosteroids (ICS) alone or in combination with a long-acting β2-agonist (LABA) contributes to 34% of asthma deaths in the United Kingdom.[7] Treatment adherence can be monitored subjectively using validated questionnaires, or objectively by using different methods, including drug dose counting, prescription possession ratios and measuring drug levels in the blood or urine.[8]

Electronic methods offer a potential solution to improving adherence to asthma medication. The WHO's definition of 'eHealth' is the use of health information and communication technologies (ICT) that include treatment, research, education of HCP, public health monitoring and a variety of technological interventions. The umbrella of eHealth includes Telehealth (telephonic or electronic technology for long-distance healthcare monitoring) or electronic monitoring devices (EMDs) (eg, a propeller that includes a sensor and mobile app), mHealth (clinical intervention by mobile devices and text message reminders) and social media (incorporating an interactive web-based platform).[9] Digital health is a new term that includes electronic interventions for health and innovative forms of ICT to address health needs. Digital health contributes to monitoring adherence that is highly customisable low cost and easily accessible. The terms eHealth and digital health are often used interchangeably. However, their intended meaning may vary. eHealth refers to the provision of high-quality care for an increasing number of people and doing so cost-effectively and efficiently. Digital health indicates the use of electronic tools to address health needs and is considered the umbrella label for a wide range of technological interventions that could meet the healthcare challenges of the present consumer-driven to include digital consumers.[10 11]

Electronic methods can improve adherence to asthma medications, which may not necessarily translate to improved clinical outcomes.[12] Electronic methods of monitoring patients with asthma have increased rapidly in the last decade, particularly during the COVID-19 pandemic. However, their effectiveness and utility in asthma remain uncertain. Electronic methods may reveal different outcomes such as improved adherence and asthma control or poor adherence and poor control in which case adherence improvement will be required. However, in cases of persistent poor asthma control despite good adherence, treatment step-up, including initiation of biologic treatment in severe asthma will be required to improve asthma outcomes and control.[13]

In this systematic review, published peer-reviewed studies were examined to provide the best current evidence on the use of electronic methods compared with standard therapy (without electronic technology). Since the optimal method for monitoring adherence to regular ICS alone or in combination with an LABA remains unclear, this study aimed to evaluate the effectiveness of electronic methods in monitoring and enhancing adherence to regular ICS alone or in combination with an LABA and any consequent effect on asthma clinical outcomes.

Objectives

- To conduct a systematic review to identify and evaluate the current published peer-reviewed studies on various electronic methods used to monitor adherence to regular ICS alone or in combination with LABA in adults and children with asthma.
- To assess the effectiveness of various electronic methods in monitoring the adherence to regular ICS alone or in combination with LABA versus conventional care or placebo by comparing the mean difference of medication adherence rates.
- To compare the various electronic methods to monitor the adherence to regular ICS alone or in combination with LABA with changes in adherence rates and associated asthma-related clinical outcomes, such as asthma control, asthma exacerbations, emergency visits or oral corticosteroid use.
- To provide an evidence-based recommendation for the optimal electronic method/s for monitoring adherence to regular ICS alone or in combination with LABA by comparing the performance of published electronic methods to conventional care or placebo.
- To identify and report on current gaps in the literature on the use of these technologies and recommend future research requirement.

METHODS

Design

A narrative systematic review.

Setting

There were no boundaries by type of setting.

Study eligibility criteria

Study design

A narrative systematic review including papers with either or both qualitative and quantitative outcomes.

Inclusion criteria

All eligible published peer-reviewed studies not in exclusion criteria were included with no restrictions on the

study design, or language to minimise bias while collating and synthesising evidence from all the relevant literature.

Exclusion criteria

Abstract-only articles, articles not reporting research design or methodologies and descriptive/editorials/opinion articles. Multiple reports of the same study included in the systematic reviews were excluded before the data collection process.

Participants

The study included children and adults (age range of 2–98 years) with a confirmed diagnosis of asthma of any type or grade as defined by the Global Initiative for Asthma guidelines who are prescribed regular ICS alone or in combination with a LABA.

Interventions

Interventions of interest included electronic methods with/without an audio-visual reminder function, online apps, short message service reminder functions or data recording or any additional electronic intervention, which allows HCP to provide adherence feedback. Studies using electronic methods to measure adherence for non-electronic adherence interventions were not considered.

Comparators

For patients prescribed regular ICS alone or in combination with an LABA, reports involving their routine non-electronic monitoring intervention or placebo groups without monitoring adherence were used as comparators.

Primary outcomes

The primary outcomes of interest were the effect of electronic methods on medication adherence rates to regular ICS alone or in combination with an LABA, asthma control (measured using clinically validated questionnaires, eg, asthma control test (ACT) or asthma control questionnaire (ACQ)) and the number of asthma exacerbations as defined by hospital admissions or treatment with oral corticosteroids.

Secondary outcomes

The secondary outcomes involved exploring the effect of electronic methods on the forced expiratory volume (FEV_1), peak expiratory flow rate, fraction-exhaled nitric oxide (FeNO), days of missed school or work, cost of interventions, patient satisfaction and adverse events/side effects.

Study appraisal and synthesis methods

This systematic review was completed according to a predetermined protocol with prespecified eligibility criteria to identify information relevant to the research question and associated study objectives. The study protocol was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-P statement and registered in the International Prospective Register of Systematic Reviews (PROSPERO) database. The present systematic review is reported using the PRISMA Checklist (online supplemental appendix 1).

Databases

The databases included were MEDLINE (OVID interface, 1948 onwards), EMBASE (OVID interface, 1980 onwards), Cochrane Database of Systematic Reviews and Web of Science. The decision to use these sources was agreed by a group of asthma experts and a professional librarian at the University of Birmingham (UK) to ensure comprehensive outputs. To maximise the search results, all published studies were searched without time or language limitations, and output reference lists were inspected for additional relevant studies. Authors' personal files were also examined to collect all relevant studies. Rayyan software[14] was used to screen the titles and abstracts of identified studies based on the eligibility criteria. Studies were grouped according to their outcome in a tabulated form to allow for semiqualitative comparisons. All results were reported in the context of overall study quality.

Search strategy

A three-step comprehensive search strategy was conducted to identify peer-reviewed studies comparing the effectiveness of electronic methods compared with conventional care or placebo in monitoring the adherence to regular ICS alone or in combination with a LABA. Initially, MA suggested predefined search terms and combinations with database-specific standard vocabulary based on the indexing methodology used by each specific database (online supplemental appendix 2). A systematic and comprehensive literature search was then conducted using MEDLINE, EMBASE, Cochrane Database of Systematic Reviews and Web of Science combining three concepts: asthma, adherence and electronic. A second step involved consulting a group of asthma experts and professional librarians at the University of Birmingham (UK) to further develop the search strategy. The resultant strategy was used to conduct the systematic review: an update was conducted before data synthesis in July 2022 to ensure that the maximum number of relevant outputs were retrieved.

Study records

Data management

Searches were downloaded and duplicates were removed using Zotero V.5.0 software. Two researchers (MA and AM) independently screened titles and abstracts and assessed studies for inclusion against eligibility criteria. Potentially eligible studies were ordered as a full text and reviewed independently by the primary researcher (MA). Disagreements were referred to a third researcher (JFM). The numbers of studies included and excluded at all stages are shown in figure 1.

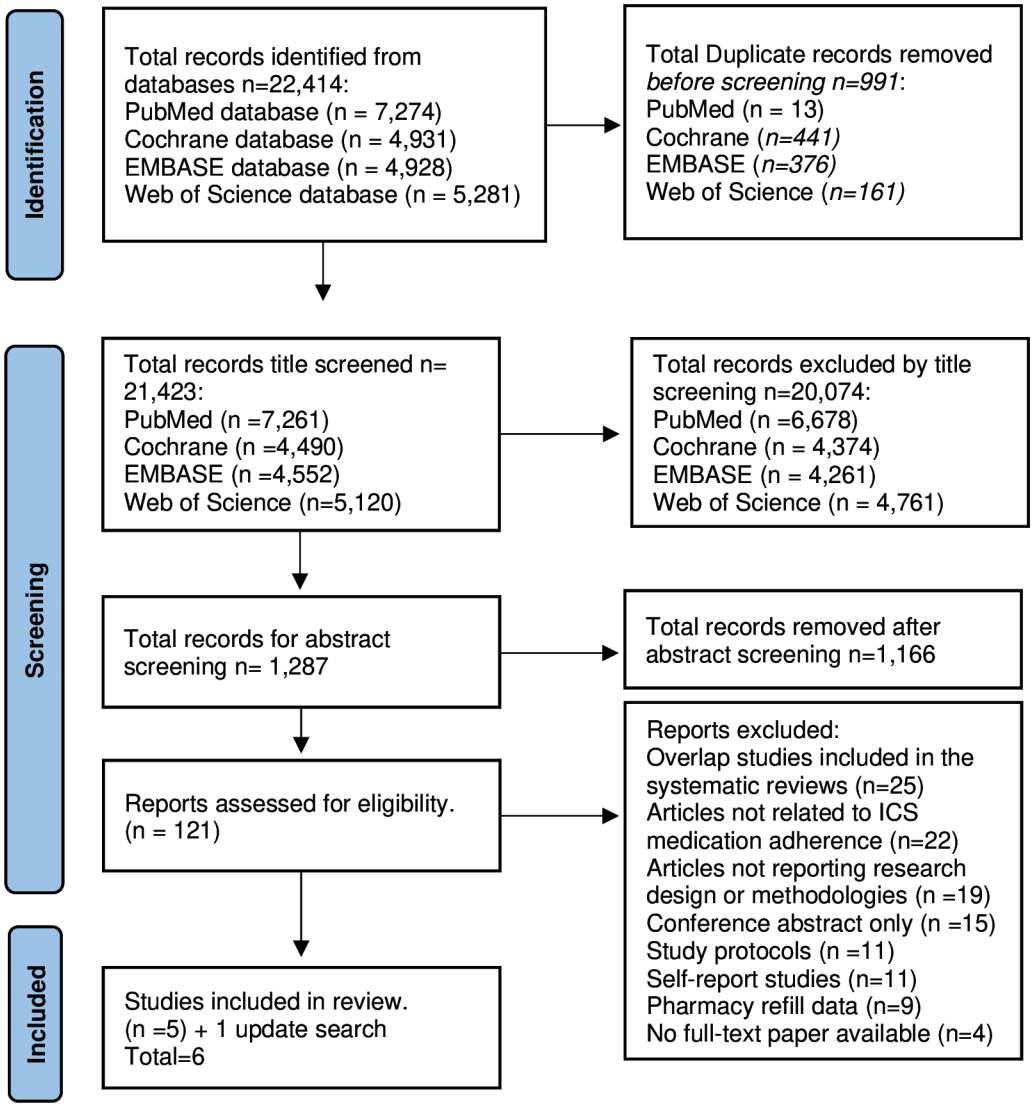

Figure 1 Study identification and selection process. The flow of information through the different stages of the systematic review and meta-analysis according to PRISMA guidelines. ICS, inhaled corticosteroids; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Selection process

Data collection process

Data extraction was conducted by the primary researcher (MA) and checked and agreed on by two researchers (AM and JFM). Data extraction was performed according to a predetermined data extraction sheet specific to the review objectives (online supplemental appendix 3). The predetermined data extraction table was reviewed and agreed on by two researchers before use. For consistency and clarity, differences were resolved at a consensus meeting of all authors.

Data items

Extracted data included the study description, search strategy, intervention, comparator, outcome measures, risk of bias, study findings and any additional information (online supplemental appendix 4). One researcher completed data extraction (MA) and a second researcher cross checked the results (AM). Discrepancies were cross checked by a third researcher (JFM) to reach a consensus agreement.

Data synthesis

Meta-analysis was not possible based on the findings of the scoping search; however, a narrative systematic review was performed to allow for grouping of results based on asthma inhaler adherence rates, asthma control and exacerbations.

Standardised mean difference

The standardised mean difference (SMD, Cohen's d) was used to provide an estimate of effect of pooled data from multiple studies using different tools to measure outcomes of interest. SMD tends to overestimate the effect size, especially when the sample size is small (<20). SMD values of 0.2, 0.5 and 0.8 represented small, medium and large effects, respectively. If two normally distributed populations were equal in size and variability, then,

a d=0.2 would imply about 85% overlap between these populations, which makes it hard to differentiate between them. When d=0.5, the overlap shrinks to about 67%, and the difference between these populations becomes apparent, while with d=0.8, the overlap shrinks to about 53%, leading to a clear differentiation.[15] In this systematic review, we used Cohen's d to compare the effect estimates of various adherence assessment tools used in monitoring adherence as an outcome. We opted for this approach as SMD tends to overestimate the effect size, particularly in small sample size studies.

Risk of bias in individual studies

Randomised controlled trials

The quality of each randomised controlled trial (RCT) found was assessed independently by the main researcher (MA) using the Cochrane Risk of Bias Tool. The tool is selected to promote consistency in quality assessments across systematic reviews, specifically assessing the methodological risk of bias within RCTs since it has been shown to exhibit acceptable inter-rater reliability (ICC=0.58, 95% CI 0.20 to 0.81).[16] The RCTs were assessed based on six risks of bias domains:

1. Sequence generation.
2. Allocation concealment.
3. Blinding of participants.
4. Incomplete outcome data.
5. Short-term selective outcome reporting and long-term selective outcome reporting.
6. Any other sources of bias.

Systematic review studies

The quality of each systematic review found was assessed independently by the main researcher (MA) using the Risk of Bias in Systematic Reviews (ROBIS) tool[17] with discrepancies being resolved by author group discussion. The output assessments included three phases of, evaluating the study relevance, identifying concerns with the review process and judging the risk of bias. Phase 2 assessed four domains: the study eligibility criteria, identification and selection of studies, data collection and study appraisal and data synthesis and findings. Phase 3 includes summarising the concerns identified during the phase 2 and judging the risk of bias.

Patient and public involvement

This systematic review examined previously published literature to comprehend and convey the priorities and experiences of individuals with asthma without the direct involvement of patients or the public.

Data availability statement

No additional data are available.

RESULTS

Study selection and characteristics

The comprehensive literature search yielded 22 414 articles identified through four databases. The study selection process is outlined in figure 1. A total of 991 duplicate articles were removed before title screening. After screening titles, 20 074 articles were excluded by title screening because the topic was not relevant to the study approach. Based on abstract screening, 1166 articles were excluded for reasons, including descriptive studies having no adherence outcomes measured, editorials, opinion papers and studies that included oral asthma or non-asthma medications. After screening abstracts, 121 articles were eligible for full-text review of which only six published articles (five systematic reviews and one RCT) were eligible for inclusion in this study narrative review synthesis.[18–23] Reasons for exclusions included overlap studies appearing in included systematic review outputs, articles not related to ICS adherence (eg, diagnosis, feasibility), articles not reporting research design or methodologies, availability restricted to a conference abstract, articles only reporting study protocols, self-report studies, pharmacy refill data or no full-text paper available.

The five systematic reviews in the narrative synthesis comprised 97 studies. Most of the systematic reviews (three out of five) were performed on children with asthma, including one systematic review of children with severe asthma, while the other two included asthmatic children and adults. The included RCTs enrolled a wide age range of patients with asthma (2 to 98 years). The types of electronic technology methods included in the narrative synthesis were eHealth in two studies, digital health in one study, mHealth in three studies, and four studies evaluated EMDs. Sample sizes varied from 93 to 3913 children and 55 asthmatic adults, and 15 207 combined asthmatic children and adults published from 1998 to 2022, covering studies in the USA, Canada and the United Kingdom. The results are summarised in online supplemental table 1.

Effect of the type of the electronic method

eHealth interventions

The comparison of all categories of eHealth technologies among adults and children in monitoring adherence versus control yielded a small effect in the meta-analysis study conducted by Jeminiwa *et al* (SMD 0.41, 95% CI 0.02 to 0.79). The level of heterogeneity between eHealth technologies in adherence results was high (I^2=98%), and subgroup differences were statistically significant (χ^2=8.46, df=2, p=0.01). When the adherence effects were analysed based on the type of eHealth technology used to monitor adherence, they were significant in studies using EMDs (SMD 1.19, 95% CI 0.49 to 1.89) but insignificant in those using pharmacy refill data (SMD −0.13, 95% CI −0.70–0.44) or self-reports (SMD 0.25, 95% CI −0.10–0.60). Analysis of five pooled studies among adults and children on adherence to ICS, including social media via an interactive platform, electronic health records, interactive voice response (IVR), speech recognition and telephone calls by health professionals against control, resulted in insignificant effects on adherence (SMD 0.20, 95% CI −0.02–0.43) (p=0.07).[20] A narrative-systematic review conducted

by Pearce *et al* among children with asthma included one study evaluating a web-based interactive education and monitoring system based on social cognitive theory and eHealth theoretical models compared with receiving an asthma education manual among 42 asthmatic children. Compared with the baseline adherence rate for both groups (38%), the mean change in adherence increased by 11.2% in the intervention group to a 4.4% decrease in the control group (p=0.67).[21]

Electronic monitoring devices

A meta-analysis by Chan *et al* included seven studies and conducted analysis by the type of electronic technology among children and adults and observed statistically significant improvement in adherence in the EMD group compared with the control group with a mean difference (MD 23% higher, 95% CI 10.84 to 34.16) (p=0.0002).[19] A narrative-systematic review by Pearce *et al* included three studies evaluating EMDs among children. Two studies compared EMDs with feedback versus EMDs alone. One study showed 70% versus 49% median adherence for the intervention group (p<0.001)[24] and the second study showed 79% versus 57.9% for the intervention group (p<0.01).[25] The third study compared the adherence interventions among asthmatic children with EMDs with audio-visual enabled (intervention group) to EMDs with audio-visual disabled (control group) every 2 months for 6 months period.[26] The median adherence in the intervention group was 84% (10th/90th percentile 54%–96%), compared with 30% in the control group (10th/90th percentile 8%–68%), p<0.0001.[21] A meta-analysis of 10 RCTs by Lee *et al* evaluated EMDs with clinical feedback compared with usual care or placebo group among 1123 asthmatic children and revealed that the EMD group was 1.50 times (RR=1.50, 95% CI 1.19 to 1.90) more likely to adhere to inhaler therapy compared with the control group (p<0.001) with medium-to-large effect size (g=0.64). However, there were no significant differences in asthma exacerbation events per year (risk ratio 0.89, 95% CI 0.45 to 1.75) (p=0.72), or asthma control using ACQ scores (Z=−0.91, p=0.36) and ACT scores (Z=0.95, p=0.34) when compared with control, but one clinical trial showed a significant improvement in children ACT scores in the intervention group than the control group (p=0.02) with a small effect size (g=0.33).[22] The Boutopoulou *et al*'s systematic review was conducted to assess interventions on adherence to treatment in children with severe asthma and included a prospective median of 92 days observational cohort study that evaluated the adherence rate of 93 outpatient severe asthmatic children by an EMD (5–17 years old).[13] The adherence rate improved from a baseline range of adherence rate from 21%–99% (median 74%) to ≥80% adherence rate for 39 patients, 60%–79% adherence rate for 25 patients (42%), and <60% adherence rate for 29 patients (31%). However, suboptimal adherence (adherence rate <80%) remained prevalent among all children with severe asthma representing 58%.[18] A randomised clinical trial conducted by Berg *et al* compared the monitoring of adherence to any inhaled asthma medications through paper diary records and EMDs using the metered dose inhaler (MDI) Chronolog among 55 adult asthmatic patients. The MDI Chronolog records the date and time of each inhaled activation. The self-report measure used was a daily asthma paper diary. Adherence rates measured by EMDs (MDI Chronolog) showed 26% of the experimental group had >80% adherence rates versus 4% in the control group, although in each case, self-reported compliance was higher than the monitored adherence.[23]

mHealth (Text message services)

Four studies included in the meta-analysis conducted by Chan *et al* demonstrated that using a short text message service had improved adherence to therapy in children and adults with asthma compared with controls, with a mean difference (MD 12%, 95% CI 6.22 to 18.03) (p=0.0001).[19] Jeminiwa *et al*'s quantitative analysis of the mHealth application in the form of text messages, either primarily or as an adjunct reminder and an audio-visual reminder, demonstrated overall improvements in adherence to ICS among adults and children across different methods used for adherence monitoring (SMD 0.96, 95% CI 0.28 to 1.64). The adherence improvement in studies utilising EMDs to monitor adherence was 1.28, 95% CI 0.41 to 2.14, and in those using self-reports was 0.52, 95% CI 0.23 to 0.82.[20] A further narrative-systematic review among children with asthma by Pearce *et al* included one study on automated text message reminder interventions. The mHealth intervention group had a text message reminder, each with a tip about the value of regular controller use, compared with a control group who received only two reminders to synchronise their sensors for 30 days.

The mean adherence rates during the 30-day intervention were 34% for the intervention group and 40% for the control (p=0.56). There was also no significant difference between the intervention and control groups after adjusting for age and parental education, with none of the cases exceeding the 80% adherence threshold (control=32% vs intervention=36%, p=0.73).[21]

Digital interventions

The most recent systematic review and meta-analysis by Chan *et al* evaluated published articles up to June 2020 and assessed the effectiveness of various digital technologies among children and adult asthmatic patients. The digital intervention group showed a mean adherence percentage improvement of MD of 14.66% (95% CI 7.74 to 21.57) as compared with a control group without digital interventions. The heterogeneity of digital technologies in adherence results was high (I^2=94%) (I^2 value of 75% to 100% represents considerable heterogeneity).[27] The various scales of asthma control among the digital interventions group showed a small improvement effect than the control group, with a 67% to 85% overlap between the two groups (SMD 0.31, 95% CI 0.17 to 0.44). There

Table 1 Risk of bias using Cochrane risk-of-bias tool

RCT	Sequence generation	Allocation concealment	Blinding of participants	Incomplete outcome data	Short-term and long-term selective outcome reporting	Any other sources of bias	Overall
Berg *et al*[23]	Some concerns	Some concerns	Some concerns	High	Low	Low	Some concerns

RCT, randomised controlled trial.

was also a small improvement in asthma-related quality of life in the digital interventions group to the control group and again demonstrated an overlap of 67%–85% between the two groups (SMD 0.26, 95% CI 0.07 to 0.45) (p=0.007).

The number of patients with ≥1 asthma exacerbation was reduced by 47% in the digital interventions group compared with the control (risk ratio 0.53, 95% CI 0.32 to 0.91) (p=0.02). However, there were no significant differences in FEV_1, and there were no data on missed school or workdays, cost-effectiveness or adverse events.[19]

Quality assessment

Quality assessment of randomised the clinical trial

The quality assessment of the RCT was assessed using the Cochrane risk-of-bias tool.[16] The findings for the risk-of-bias summary are shown in table 1. Berg *et al* reported an overall 'some concerns' bias since the measurement of the outcome could have been influenced by the knowledge of the adherence intervention received.

Quality assessment of the systematic reviews

The quality assessment of each included systematic review was assessed independently by the main researcher using the ROBIS tool.[17] The findings for the risk-of-bias summary are shown in table 2. The majority (80%) of the systematic reviews have a low risk of bias across the four domains. Boutopoulou *et al* had an overall 'high risk' bias since, insufficient details were provided about the included studies eligibility criteria, study populations or study designs. Some risk of bias may have been introduced through the data collection or assessment processes.

DISCUSSION

Electronic methods (eHealth and digital) demonstrated benefits in monitoring and improving adherence rates to inhaled asthma medications in six published articles (five systematic reviews and one RCT) comprising 98 studies published from 1998 to 2022 in the USA, Canada and UK. Distinguishing between the electronic methods utilisation in primary and hospital care is challenging due to the diverse healthcare systems the data obtained from. Children were the primary focus of the reviews due to their inclusion in all of them, with only two covering adults and children. The broad age range of 2–98 years strengthens the generalisability of these results since no significant differences were found for the participant age range of 2–98 years for a total of 15 207 participants from 30 studies. EMDs were the most promising electronic technology demonstrating an average improvement in adherence rate of 23%, with children being 1.5 times more likely to adhere to their inhalers than non-EMD users with medium-to-large effect size (g=0.64). Adherence rates were also improved using mHealth (text message services) by an average of 12%. The effectiveness of asthma-related clinical outcomes was small, manifesting a small to medium effect for various asthma control scales (SMD=0.31) and a small effect in asthma-related quality of life (SMD 0.26) (p=0.007). There is still uncertainty regarding the effectiveness of electronic methods in reducing asthma exacerbations. There was variation in exacerbation reduction 'between the studied interventions' that ranged from a significant reduction of 47% (p=0.02) to a non-significant reduction of 11% (p=0.72), thus arguing for further studies to confirm or

Table 2 Risk of bias using ROBIS tool

Systematic reviewee	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	Risk of bias in the review
Lee *et al*[22]	Low	Low	Low	Low	Low
Jeminiwa *et al*[20]	High	Low	Low	Low	Low
Pearce *et al*[21]	Low	Low	Low	Low	Low
Boutopoulou *et al*[18]	High	High	High	Low	High
Chan *et al*[19]	Low	Low	Low	Low	Low

ROBIS, Risk of Bias in Systematic Reviews.

Table 3 Description of electronic technologies for monitoring adherence to inhaled asthma medications

eHealth	Digital health
eHealth: The use of technologies in public health cost-effectively to include the following: ► **MHealth:** clinical interventions supported by mobile devices to include text messages, or audiovisual reminders. ► **Telehealth:** long-distance intervention technology used to clinical healthcare needs to include HCP telephone calls, interactive voice response (IVR) systems. ► **Electronic health records (EHRs):** Electronic interventions that use electronic health records for patient care. ► **Electronic monitoring devices (EMDs):** Electronic devices used with inhalation devices to measure time, location and activation or actuation of the device. ► **Social media:** An interactive platform intervention/online community to share and discuss user-generated content.	**Digital health:** The use of technologies in public health from a consumer perspective to include the following: ► **Web-based platforms:** online web browser intervention usually via a computer device and Internet connection, referred to as 'e-health'. ► **Computer-based platforms**: computer-based platforms via a computer device, mobile, or tablet that do not require Internet connection. ► **Mobile applications:** software mobile programs that interact with users via a set of interfaces, but internet connection is not always required, referred to as 'M-health'. ► **Short message services (SMS):** mobile phone text messages or text messages platforms such as WhatsApp, with the aim of improving adherence by sending education messages or reminders. ► **Computer games:** Interactive game- based interventions to influence behaviour, particularly for adolescents. ► **IVR systems:** A computer-linked telephone system to make automated phone calls to promote adherence. ► **EMDs:** Electronic devices used with inhalation devices to measure time, location and activation or actuation of the device. ► **Telephone-based interventions:** HCP telephone calls, telemonitoring or telehealth.

HCP, healthcare professional.

refute this effect. The effectiveness of electronic methods in improving asthma control and quality of life remains small since their evidence base is uncertain. While this systematic review brings a unique summary of systematic reviews in one place, it highlights the inconsistency and overlapping use of terminology describing electronic methods for monitoring adherence (see table 3). In this review, we found little data on the utility of electronic devices in adherence management in severe asthma and no data on the cost-effectiveness of such EMD clinical use.

EMDs showed the most promising adherence improvement than other electronic methods. EMDs record daily usage and exchange data via mobile applications and a website platform between patients with asthma and HCP, which varies from using the EMDs alone.[28] This connected inhaler system (CIS), such as those of the SmartInhaler (Adherium) and Propeller Health, uses sensors connected to an inhaler device that transmits drug usage details via the Bluetooth system to an application on a patient smartphone, which in turn shares such data on a web platform that is accessible to the HCP, thus providing objective and live adherence data. The CIS (EMD+HCP feedback) achieved higher adherence rates (mean adherence 79% vs 57.9%) (p<0.01) and (median adherence 70% vs 49%) (p<0.001). Moreover, some EMDs use acoustic technologies to ascertain actual drug inhalation and inhalation technique, which may overcome dose dumping issues and provide HCP feedback on inhaler technique issues SmartInhaler (Adherium). EMDs have been combined with an asthma biomarker in the form of exhaled fractional nitric oxide (FeNO) for adherence monitoring (FeNO suppression test). This method can detect non-adherence by identifying previously non-respondents that respond well to an EMD-monitored high-dose ICS therapy, compared with non-respondents, despite the adequate level of adherence (ICS resistant) who may require alternative treatments such as escalation to biologic therapy.[29] Owing to improved adherence to ICS and consequent improvement in asthma control, the FeNO suppression test led to significantly fewer patients with uncontrolled asthma progressing to biologic therapy.[8] Although EMDs improve adherence, the associated costs of using EMDs with extra/fewer resources allocated by more/less GP/pharmacist/nurse visits for data collection and interpretation need to be considered.[30] Considering the direct/indirect cost of adherence visits, time and the cost of the devices, affordability needs to be evaluated, using this technology in monitoring adherence. MHealth (text messages) showed adherence improvement, particularly among adolescents. This population benefited from this type of reminder system by being more proficient users of text messaging and reported the usefulness of a text messaging reminder system for asthma.[31] However, it is also uncertain whether adherence improvement will remain after the patients with asthma recognise, they are not monitored. A web-based interactive education and monitoring system by education, self-monitoring and rewards showed an insignificant adherence effect compared with only receiving an asthma education manual (p=0.67). Moreover, studies using pharmacy refill data or self-report, electronic health records, IVR and HCP telephone calls did not show a significant adherence effect.[21]

The advent of electronic methods in asthma management was associated with a small improvement in asthma-related clinical outcomes and quality of life in most

studies. Such observed effect may be related to the significant heterogeneity of studies and technologies used in the literature. In addition, electronic methods associated improvement in adherence may still be variable and inadequate, thus not reaching the required level to affect the necessary improvement in asthma outcomes. Inadequate adherence is common in asthma.[32] An adherence rate of 80% is suggested to improve asthma control and reduce exacerbations and oral corticosteroid use.[33 34] Also, other disease factors such as asthma severity or comorbidities associated with asthma may have contributed to the small observed clinical improvements. Furthermore, the variability in the adherence intervention periods among different studies that ranged from 3 weeks to 24 months, meant a significant variation in adherence rates and any consequent clinical effect.[20] Although the small improvement in asthma clinical outcomes logically would be more likely to relate to improvement in adherence rates, a Hawthorne effect, where awareness of being monitored alone can lead to clinical improvement, could not be ruled out.[35]

Electronic methods yielded variable adherence effects ranging from small–large (eHealth (SMD 0.41, 95% CI 0.02 to 0.79)), and a wide range adherence improvement rate (digital (MD 14.66% higher, 95% CI 7.74 to 21.57)). There was also significant heterogeneity in studies reporting adherence results (eHealth I^2=98%, digital I^2=94%). Absence of standardisation of terminology to describe electronic methods may contribute to such variation.[36 37] Significant overlap is evident among eHealth and digital health technologies in monitoring adherence since various electronic technologies fall under the umbrella of eHealth and digital health with mutually inclusive variations in the electronic technologies (see figure 2). Although eHealth includes public health monitoring cost-effectively and digital health includes using online platforms to address health needs from a consumer perspective, various technologies with variable performance that fall under eHealth and the digital umbrella require standardisation. This variability makes it challenging to classify them into specific groups and highlights the need for future research to improve classification clarity in this area. Developing a standardised definition of electronic methods for monitoring inhaled asthma medication is needed to improve comparisons between such technologies and to study their cost-effectiveness.[38 39]

CONCLUSION

Electronic methods have shown a consistently positive effect on monitoring adherence to inhaled medications in

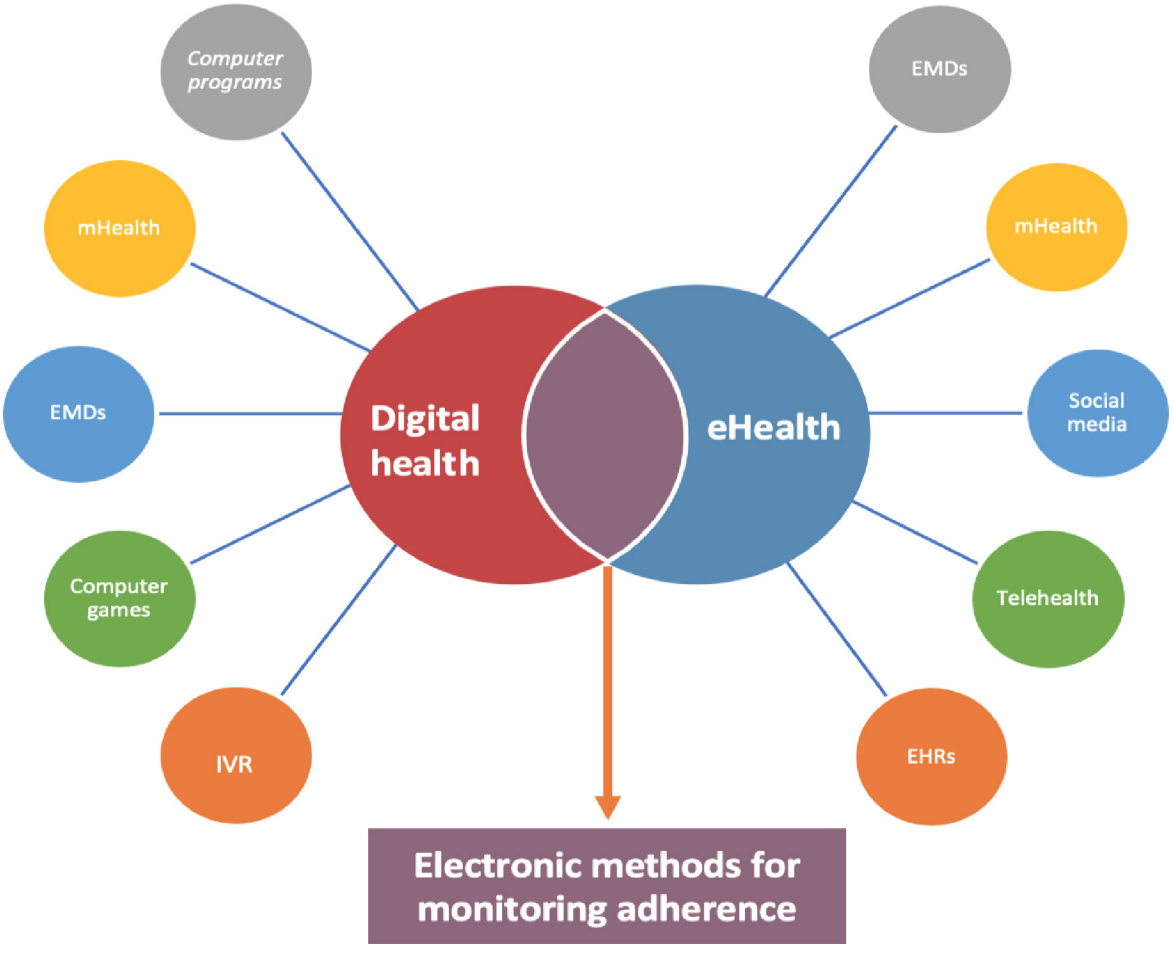

Figure 2 Electronic technologies for monitoring adherence to inhaled asthma medications.

patients with asthma. EMDs are the most promising effective technology among children and adults with asthma, followed by mHealth. Adherence improvement was associated with small clinical improvement and asthma-related quality of life. The absence of a uniform definition of electronic methods with the variation of electronic technologies needs to be standardised, working towards a more unified electronic method. The current gaps in the literature on using electronic methods include the heterogeneity of electronic technologies used in monitoring adherence. The absence of research data on cost-effectiveness studies focusing on severe asthma patients highlights the need for further research in this field.

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Supplementary

Appendix 1: PRISMA Checklist, The effect of monitoring adherence to regular inhaled corticosteroid (ICS) alone or in combination with a long-acting β2-agonist (LABA) using electronic methods on asthma outcomes: a narrative systematic review

		Reporting Item	Page Number
Title			
Title	#1	Identify the report as a systematic review	1
Abstract			
Abstract	#2	Report an abstract addressing each item in the PRISMA 2020 for Abstracts checklist	1
Introduction			
Background/rationale	#3	Describe the rationale for the review in the context of existing knowledge	2-3
Objectives	#4	Provide an explicit statement of the objective(s) or question(s) the review addresses	3
Methods			
Eligibility criteria	#5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses	4
Information sources	#6	Specify all databases, registers, websites, organisations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted	6
Search strategy	#7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used	6
Selection process	#8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and, if applicable, details of automation tools used in the process	7
Data collection process	#9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and, if applicable, details of automation tools used in the process	7
Data items	#10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in	7

		each study were sought (for example, for all measures, time points, analyses), and, if not, the methods used to decide which results to collect	
Study risk of bias assessment	#11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and, if applicable, details of automation tools used in the process	7-8
Effect measures	#12	Specify for each outcome the effect measure(s) (such as risk ratio, mean difference) used in the synthesis or presentation of results	7
Synthesis methods	#13a	Describe the processes used to decide which studies were eligible for each synthesis (such as tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5))	8
Synthesis methods	#13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics or data conversions	7
Synthesis methods	#13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses	7
Synthesis methods	#13d	Describe any methods used to synthesise results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used	7
Synthesis methods	#13e	Describe any methods used to explore possible causes of heterogeneity among study results (such as subgroup analysis, meta-regression)	7
Synthesis methods	#13f	Describe any sensitivity analyses conducted to assess robustness of the synthesised results	7
Reporting bias assessment	#14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases)	7-8
Certainty assessment	#15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	7-8
Data items	#10b	List and define all other variables for which data were sought (such as participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information	7

Results			
Study selection	#16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram (http://www.prisma-statement.org/PRISMAStatement/FlowDiagram)	8-9
Study selection	#16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded	8-9
Study characteristics	#17	Cite each included study and present its characteristics	10-12
Risk of bias in studies	#18	Present assessments of risk of bias for each included study	15-16
Results of individual studies	#19	For all outcomes, present for each study (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (such as confidence/credible interval), ideally using structured tables or plots	10-15
Results of syntheses	#20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies	N/A (narrative approach)
Results of syntheses	#20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (such as confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect	N/A (narrative approach)
Results of syntheses	#20c	Present results of all investigations of possible causes of heterogeneity among study results	N/A (narrative approach)
Results of syntheses	#20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesised results	N/A (narrative approach)
Risk of reporting biases in syntheses	#21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed	N/A (narrative approach)
Certainty of evidence	#22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	N/A (narrative

			approach)
Discussion			
Results in context	#23a	Provide a general interpretation of the results in the context of other evidence	16
Limitations of included studies	#23b	Discuss any limitations of the evidence included in the review	18-19
Limitations of the review methods	#23c	Discuss any limitations of the review processes used	18-19
Implications	#23d	Discuss implications of the results for practice, policy, and future research	19
Other information			
Registration and protocol	#24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered	19
Registration and protocol	#24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared	19
Registration and protocol	#24c	Describe and explain any amendments to information provided at registration or in the protocol	19
Support	#25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review	19
Competing interests	#26	Declare any competing interests of review authors	19
Availability of data, code, and other materials	#27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review	n/a

Appendix 2: Draft electronic search strategy

Database	#	Index and keyword terms
Cochrane	#1	MeSH descriptor: [Asthma] explode all trees
	#2	(asthma* OR wheez* OR bronchospasm OR bronchoconstrict* OR "bronchial hypersensitiv*" OR "bronchial hyperreactiv*" OR "bronchial hyperresponsiv*" OR "bronchial allerg*" OR "bronchial constrict*" OR "respiratory hypersensitiv*" OR "respiratory hyperreactiv*" OR "respiratory hyperresponsiv*" OR "respiratory allerg*" OR "respiratory constrict*" OR "airway hypersensitiv*" OR "airway hyperreactiv*" OR "airway hyperresponsiv*" OR "airway allerg*" OR "airway constrict*"):ti,ab,kw
		#1 OR #2
	#3	MeSH descriptor: [Metered Dose Inhalers] this term only
	#4	MeSH descriptor: [Dry Powder Inhalers] this term only
	#5	(inhal* OR "inhaled corticosteroid*" OR "inhaled steroid*" OR "asthma* control*
	#6	medication*" OR "asthma* reliever medication*"):ti,ab,kw
		#4 OR #5 OR #6
	#7	(electronic OR digital OR technolog* OR device* OR audiovisual OR monitor* OR
	#8	emd* OR record* OR intervention* OR remind* OR "adherence digital monitor*" OR "adherence electronic monitor*" OR smart OR track* OR datalog* OR mdilog* OR "mdi chronology" OR propeller):ti,ab,kw
	#9	#7 AND #8
	#10	#3 AND #9
PubMed		((("Asthma"[Mesh]) OR ((asthma*[Title/Abstract] OR wheez*[Title/Abstract] OR bronchospasm[Title/Abstract] OR bronchoconstrict*[Title/Abstract] OR "bronchial hypersensitiv*"[Title/Abstract] OR "bronchial hyperreactiv*"[Title/Abstract] OR "bronchial hyperresponsiv*"[Title/Abstract] OR "bronchial allerg*"[Title/Abstract] OR "bronchial constrict*"[Title/Abstract] OR "respiratory hypersensitiv*"[Title/Abstract] OR "respiratory hyperreactiv*"[Title/Abstract] OR "respiratory hyperresponsiv*"[Title/Abstract] OR "respiratory allerg*"[Title/Abstract] OR "respiratory constrict*"[Title/Abstract] OR "airway hypersensitiv*"[Title/Abstract] OR "airway hyperreactiv*"[Title/Abstract] OR "airway hyperresponsiv*"[Title/Abstract] OR "airway allerg*"[Title/Abstract] OR "airway constrict*"[Title/Abstract])))) AND ((((("Metered Dose Inhalers"[Mesh] OR "Dry Powder Inhalers"[Mesh])) OR ((inhal*[Title/Abstract] OR "inhaled corticosteroid*"[Title/Abstract] OR "inhaled steroid*"[Title/Abstract] OR "asthma* control* medication*"[Title/Abstract] OR "asthma* reliever medication*"[Title/Abstract])))) AND ((electronic[Title/Abstract] OR digital[Title/Abstract] OR technolog*[Title/Abstract] OR device*[Title/Abstract] OR audiovisual[Title/Abstract] OR monitor*[Title/Abstract] OR emd*[Title/Abstract] OR record*[Title/Abstract] OR intervention*[Title/Abstract] OR remind*[Title/Abstract] OR "adherence digital monitor*"[Title/Abstract] OR "adherence electronic monitor*"[Title/Abstract] OR

		smart[Title/Abstract] OR track*[Title/Abstract] OR datalog*[Title/Abstract] OR mdilog*[Title/Abstract] OR “mdi chronology”[Title/Abstract] OR propeller[Title/Abstract])))
EMBASE	# 1 # 2 #3 #4 #5 #6 #7 #8 #9 #10 #11	'asthma'/exp asthma*:ti,ab OR wheez*:ti,ab OR bronchospasm:ti,ab OR bronchoconstrict*:ti,ab OR 'bronchial hypersensitiv*':ti,ab OR 'bronchial hyperreactiv*':ti,ab OR 'bronchial hyperresponsiv*':ti,ab OR 'bronchial allerg*':ti,ab OR 'bronchial constrict*':ti,ab OR 'respiratory hypersensitiv*':ti,ab OR 'respiratory hyperreactiv*':ti,ab OR 'respiratory hyperresponsiv*':ti,ab OR 'respiratory allerg*':ti,ab OR 'respiratory constric*':ti,ab OR 'airway hypersensitiv*':ti,ab OR 'airway hyperreactiv*':ti,ab OR 'airway hyperresponsiv*':ti,ab OR 'airway allerg*':ti,ab OR 'airway constrict*':ti,ab #1 OR #2 'inhaler'/exp inhal*:ti,ab OR 'inhaled corticosteroid*':ti,ab OR 'inhaled steroid*':ti,ab OR 'asthma* near/2 medication*':ti,ab #4 OR #5 electronic:ab,ti OR digital:ab,ti OR technolog*:ab,ti OR device*:ab,ti OR audiovisual:ab,ti OR monitor*:ab,ti OR emd*:ab,ti OR record*:ab,ti OR intervention*:ab,ti OR remind*:ab,ti OR 'adherence near/2 monitor*':ab,ti OR smart:ab,ti OR track*:ab,ti OR datalog*:ab,ti OR mdilog:ab,ti OR 'mdi chronolog':ab,ti OR propeller:ab,ti #6 AND #7 #3 AND #8 #9 AND #10
Web of Science	#1 #2 #3 #4 #5	TS= (asthma* OR wheez* OR bronchospasm OR bronchoconstrict* OR “bronchial hypersensitiv*” OR “bronchial hyperreactiv*” OR “bronchial hyperresponsiv*” OR “bronchial allerg*” OR “bronchial constrict*” OR “respiratory hypersensitiv*” OR “respiratory hyperreactiv*” OR “respiratory hyperresponsiv*” OR “respiratory allerg*” OR “respiratory constrict*” OR “airway hypersensitiv*” OR “airway hyperreactiv*” OR “airway hyperresponsiv*” OR “airway allerg*” OR “airway constrict*”) TS= (Inhal* OR “Inhaled corticosteroid*” OR “inhaled steroid*” OR “metered dose inhaler*” OR “dry powder inhaler*” OR “asthma* control* medication*” OR “asthma* reliever medication*”) TS= (electronic OR digital OR technolog* OR device* OR audiovisual OR monitor* OR EMD* OR record* OR intervention* OR remind* OR “adherence digital monitor*” OR “adherence electronic monitor*” OR smart OR track* OR datalog* OR MDIlog OR “MDI chronolog” OR propeller) #3 AND #2 #4 AND #1

Appendix 3: Data Extraction Sheet

Study	**Study design**	**No. of subjects**	**Population**	**Intervention**	**Comparative**	**Key Outcomes**	**Methods of adherence monitoring**	**Findings**
Berg 1998	RCT	55	Adult asthmatic patients	31 used MDI chronolog	24 used asthma diaries	Adherence score	MDI Chronotog	After a 6-week period, experimental group's adherence score increased and control group's adherence score decreased (U= 271, p=.043)
Boutopoulou 2018	SR	93	Severe outpatient asthmatic children	EMDs adherence interventions	Without adherence interventions	The influence of EMDs adherence interventions	EMDs	After six months of monitoring, baseline adherence rates 28% to 67% (control groups), after the intervention, rates increasing from 49 to 81%. Median adherence for whole population was 74%. Good adherence (≥80%) in 42% of patients, Suboptimal adherence (<80%) in 58% ($p < 0.0065$).
Jeminiwa 2019	SR & Meta-analysis	Total of 13,907 from 15 trials for qualitative synthesis and 12 trials for quantitative synthesis.	Children and adult asthmatic patients	eHealth	Usual care or without eHealth	• Effectiveness of eHealth on adherence to ICS • Types of eHealth in use	eHealth	eHealth adherence effect (SMD=0.41, 95%CI=0.02–0.79). Adherence effect in studies utilizing EMDs only as an adherence measure (SMD = 1.19, 95%CI = 0.49–1.89). MHealth adherence effect (SMD = 0.96, 95%CI = 0.28–1.64).

								MHealth adherence effect by utilizing EMDs (SMD = 1.28, 95%CI = 0.41–2.14). eHealth insignificant adherence effect in studies utilizing pharmacy refill data (SMD = −0.13, 95%CI = −0.70 – 0.44) or self-report (SMD = 0.25, 95%CI = −0.10 – 0.60), or social media, electronic health records, interactive voice response, telephone calls by health care providers (SMD = 0.20, 95%CI = −0.02 – 0.43).
Lee 2021	SR & Meta-analysis	Total of 1,123 from 10 trials	Children asthmatic patients	EMDs adherence interventions	Usual care, waitlist, or placebo	• Inhaler adherence • Clinical outcomes	EMDs	EMDs group was 1.50 times (RR = 1.50, 95% CI = 1.19–1.90) more likely to adhere to inhalers compared with the control (Z = 3.37, p < 0.001) with medium-to-large effect size (g = 0.64). C-ACT in the intervention group (Z = 2.42, p = 0.02) with a small effect size (g = 0.33). No significant differences in asthma exacerbation, lung function, or asthma control.
Chan 2022	Cochrane SR & Meta-analysis	Total of 15,207 from 30 studies	Children and adult asthmatic patients	Digital adherence intervention	Non-digital adherence intervention	• Adherence • Asthma Control • Exacerbation rate	Digital monitoring Vs. non digital monitoring	Adherence increase in poor baseline adherence patients (mean difference of 14.66

								percentage points, (95% CI 7.74 to 21.57). Asthma control increased by a small (SMD) 0.31 higher, (95% CI 0.17 to 0.44). Asthma exacerbations reduced (risk ratio 0.53, (95% CI 0.32 to 0.91). Quality increased (SMD) 0.26 higher, 95% CI 0.07 to 0.45). Adherence improved with EMDs (23 percentage points over control, 95% CI 10.84 to 34.16) Adherence improved with short message services (12 percentage points over control, (95% CI 6.22 to 18.03). No significant subgroup differences for in-person component Vs. fully electronic interventions, adherence feedback, one or multiple electronic components to the intervention, or participant age. No difference in lung function (forced expiratory volume in one second (FEV1) No data on cost-effectiveness or adverse events.

Pearce 2022	SR	Total of 3,913 from 15 trials	Children asthmatic patients	Adherence intervention to ICS with at least one outcome measure of adherence	Usual care or a basic education	adherence interventions aracteristics of successful herence interventions	Electronic adherence monitoring Vs. usual care	SmartTrack with audio-visual enabled Vs. with audio-visual disabled resulted in median adherence of 84% in the intervention group (10th percentile 54%, 90th percentile 96%), Vs. 30% in control group (8%, 68%) (p< .0001). Smartinhaler with feedback Vs. Smartinhaler alone, Smartinhaler with feedback (median adherence was 70% vs. 49% for control group) (p < .001), other study found mean percentage adherence intervention = 79% vs. control = 57.9% (p< .01). MHealth intervention Vs. control group (receiving only two reminders to sync their sensors). The unadjusted mean adherence: control = 40% vs. intervention = 34% (P = .56). A web-based interactive education and monitoring system Vs. education manual. Mean change since baseline for intervention= 11.2% increase vs. control= 4.4% decrease (p=.67).

Appendix 4: Data Extraction Sheet

Study Description	Search Strategy	Intervention	Comparator	Outcome Measures	Risk of bias	Study Findings	Electronic adherence Interventions	
							Pros (+)	Cons (-)
Impact of eHealth on medication adherence among patients with asthma: A systematic review and meta-analysis **(Jeminiwa et al., 2019a)**	A five databases search including PubMed, CINAHL, Academic Search Premier, PsycINFO, and International Pharmaceutical Abstracts (IPA) From inception until August 28, 2018	eHealth among children and adult asthmatic patients	Usual care or without eHealth intervention	• Effectiveness of eHealth on adherence to ICS • The types of eHealth in use	Clear quality appraisal of the studies	From a qualitative synthesis of 15 trials and quantitative synthesis of 12 trials, overall significant effect of eHealth interventions on adherence to ICS (SMD)=0.41, 95%CI = 0.02–0.79). Also, mHealth improved adherence VS. usual care in analysis of 4 trials (SMD=0.96, 95%CI=0.28–1.64).	**eHealth** A small effect (SMD=0.41,95%CI= 0.02–0.79) **MHealth** Effective and acceptable intervention in improving adherence in studies utilizing EMDs only as an adherence measure SMD = 1.19, 95% CI = 0.49–1.89).	**MHealth** Considered insignificant in pharmacy refill data or self-report as adherence measure. **eHealth** Insignificant effects include social media, electronic health records, interactive voice response, and healthcare telephone calls.

Interventions on Adherence to Treatment in Children with Severe Asthma: A Systematic Review **(Boutopoulou et al., 2018)**	A systematic search performed in MEDLINE, PubMed, Cochrane Library, and Scopus databases from January of 2012 to March of 2018	Children and/or adolescents with severe asthma and on medication adherence interventions.	Children and/or adolescents with severe asthma with usual care without adherence interventions	The influence of adherence intervention in improving adherence to controller inhaled medication in children with severe asthma.	No evidence of quality assessment.	One prospective observational cohort study evaluating the adherence rate of 93 severe outpatient asthmatic children for 6 months by EMDs, the baseline adherence rates ranged from 28% to 67%, after the EMDs, rates increasing from 49 to 81%.		**EMDs** After 6 months, Median adherence was 74%. Good adherence (≥80%) in 42% of patients, suboptimal adherence (<80%) in 58% ($p < 0.0065$).
Features of successful interventions to improve adherence to inhaled corticosteroids in children with asthma: A narrative systematic review **(Pearce et al., 2022)**	A systematic search performed in PubMed, Embase, Psych INFO, Medline, Web of Science, and Inter-national Pharmaceutical Abstracts databases from inception until October 3, 2020	Adherence intervention to ICS among asthmatic children.	Usual treatment or a basic education.	ICS adherence and the characteristics of successful adherence interventions.	Clear quality appraisal of the studies.	• 13 of the 25 identified studies were categorized as being highly reliable. • 9 of the 13 interventions were effective at increasing adherence. • 6 met the criteria for an adherence (the Perceptions and Practicalities Approach, PAPA) intervention.	**EMDs** • One study compared SmartTrack with audio-visual enabled Vs. audio-visual disabled with 84% median adherence in intervention group (10th percentile 54%, 90th percentile 96%), Vs. 30% in the control	**MHealth** One study compared MHealth intervention Vs. control group (receiving only two reminders to sync their sensors). The unadjusted mean adherence: control = 40% vs. intervention = 34% (P = .56). **eHealth**

						• 5 studies utilized electronic monitoring interventions: eHealth (n = 1) MHealth (n = 1) EMDs (n = 3)	group (8%, 68%) p< .0001. • Two studies compared EMDs with feedback Vs. EMDs alone, one study found increase in adherence by 21% in the EMDs with feedback group (median adherence was 70% vs. 49% (p < .001) and other study found mean adherence intervention = 79% vs. control = 57.9% (p< .01).	A study compared a web-based interactive education and monitoring system Vs. asthma education manual. Mean change since baseline for intervention= 11.2% increase vs. control= 4.4% decrease (p=.67).
Electronic adherence monitoring devices for	A systematic search using Cochrane Library,	Electronic adherence monitoring devices	Usual care, waitlist, or placebo group.	**Primary outcome** Inhaler adherence	Clear quality appraisal of the studies.	• 10 randomized controlled trials in 11 articles amongst 1123	**EMDs** Amongst 1,123 asthmatic children revealed that EMDs	

children with asthma: A systematic review and meta-analysis of randomized controlled trials **(Lee et al., 2021)**	PubMed, Embase, CINAHL, Web of Science, Scopus and ProQuest Dissertations and Theses from inception up to April 6, 2021.	attached to inhalers or built into the inhaler among asthmatic children.		**Secondary outcomes** Clinical outcomes including asthma exacerbation, lung function (FEV1), asthma control and acceptability.		participants were included in the meta-analysis. Meta-analysis revealed that the electronic adherence monitoring device group was 1.50 times more likely to adhere to inhalers compared with the control group with medium-to-large effect size (g = 0.64). • No significant subgroup differences were recognized among different parameters.	group was 1.50 times (RR = 1.50, 95% CI = 1.19–1.90) more likely to adhere to inhalers compared with the control (Z = 3.37, p < 0.001) with medium-to-large effect size (g = 0.64).	

Digital interventions to improve adherence to maintenance medication in asthma **(Chan et al., 2022)**	A search for clinical trials from the Cochrane Airways Trials Register The most recent searches on 1 June 2020, with no restrictions on language of publication.	Any digital adherence intervention among children and adult asthmatic patients	Any non-digital adherence intervention or usual care	**Primary outcomes** Adherence Asthma control Asthma exacerbations **Secondary outcomes** Unscheduled healthcare visits Time off school, work, or other commitments due to asthma Lung function Quality of life Cost-effectiveness Adverse events	Clear quality appraisal of the studies.	• 15% more people between 8% and 22% adherent by receiving digital technology Vs. without digital interventions. • Digital intervention group had better asthma control and half the risk of asthma attacks between 32% and 91%). • Quality of life and lung function, but the effect on lung function was small and may be of limited clinical relevance.	**Electronic interventions** Baseline adherence (mean difference 14.66 percentage points, 95% (CI) 7.74 to 21.57 **EMDs & MHealth** • EMDs adherence (23 percentage points over control, 95% CI 10.84 to 34.16 • MHealth adherence (12 percentage points over control, 95% CI 6.22 to 18.03; four studies) (P = 0.001). **Electronic interventions** • Asthma control Improve by (SMD) 0.31	**Electronic interventions** • Little or no difference in lung function (forced expiratory volume in one second (FEV1). • No data on cost-effectiveness or adverse events.

							higher, 95% CI 0.17 to 0.44. • Asthma exacerbations reduced (risk ratio 0.53, 95% CI 0.32 to 0.91. • Quality of life increased SMD 0.26 higher, 95% CI 0.07 to 0.45.	
Compliance with inhaled medications: The relationship between diary and electronic monitor **(Berg et al., 1998)**	A randomized, controlled study evaluating inhaler medication compliance, diary data to electronic monitoring	31 asthmatic patients were among electronic monitor using MDI Chronolog	24 asthmatic patients using daily asthma diary notes for six-week self-management program.	Adherence scores	No evidence of quality assessment.	Moderate correlations (r~ = -55, Mdnd = 95.8, Mdnc = 91.6) by comparing administrations by the Chronolog administrations reported in the subject's dairy.	**MDI Chronolog** The experimental group's adherence score increased while the control group's adherence score decreased (U= 271, p=.043).	**MDI Chronolog** Self-reported adherence was higher than monitored adherence.

Table 1 Data summary

STUDY DESCRIPTION	STUDY FINDINGS
JEMINIWA 2019 SYSTEMATIC REVIEW AND META-ANALYSIS FIVE DATABASES SEARCH FROM INCEPTION UNTIL AUGUST 2018 EHEALTH AMONG CHILDREN AND ADULT ASTHMATIC PATIENTS **VS.** USUAL CARE OR WITHOUT EHEALTH INTERVENTION **OUTCOME MEASURES** THE EFFECTIVENESS OF EHEALTH ON ADHERENCE TO ICS AND THE TYPES OF EHEALTH IN USE	**eHealth** **Pros (+)** All categories of eHealth across different technologies used for monitoring adherence yielded a small effect on adherence (SMD 0.41, 95% CI 0.02–0.79), and was more significant in studies utilizing EMDs to measure adherence (SMD 1.19, 95% CI 0.49–1.89). **mHealth** **Pros (+)** Significant effect on adherence (SMD 0.96, 95% CI 0.28–1.64) across mHealth studies using different methods in monitoring adherence and significant across mHealth studies utilizing EMDs to monitor adherence (SMD 1.28, 95% CI 0.41–2.14) and self-reports (SMD 0.52, 95% CI 0.23–0.82). **eHealth** **Cons (-)** Insignificant effect on adherence in studies utilizing pharmacy refill data to monitor adherence (SMD −0.13, 95% CI −0.70 – 0.44) or self-report (SMD 0.25, 95% CI −0.10 – 0.60), or electronic health records, interactive voice response, telephone calls by HCP (SMD 0.20, 95% CI −0.02 – 0.43).
BOUTOPOULOU 2018 SYSTEMATIC REVIEW FOUR DATABASES SEARCH FROM JANUARY 2012 TO MARCH OF 2018 MEDICATION ADHERENCE INTERVENTIONS AMONG SEVERE ASTHMA CHILDREN **VS.** WITHOUT ADHERENCE INTERVENTIONS **OUTCOME MEASURES** INFLUENCE OF ADHERENCE INTERVENTIONS	**EMDs** **Pros (+)** One prospective observational cohort study monitored adherence rates over median of 92 days interval following EMDs technology for 93 severe outpatient asthmatic children. The adherence rate baseline was (median 74% (21%-99%). Post EMDs, ≥80% adherence rate for 39 patients, 60-79% adherence rate for 25 patients (42%), and <60% adherence rate for 29 patients (31%). **`Cons (-)** Suboptimal adherence (adherence rate <80%) remained prevalent among all children with severe asthma representing 58%.

PEARCE 2022 ANARRATIVE SYSTEMATIC REVIEW SIX DATABASES SEARCH FROM INCEPTION UNTIL OCTOBER 2020 ADHERENCE INTERVENTION AMONG ASTHMATIC CHILDREN TO ICS WITH AT LEAST ONE OUTCOME MEASURE OF ADHERENCE **VS.** USUAL TREATMENT OR A BASIC EDUCATION **OUTCOME MEASURES** ICS ADHERENCE INTERVENTIONS IN CHILDREN WITH ASTHMA AND CHARACTERISTICS OF SUCCESSFUL ADHERENCE INTERVENTIONS	**EMDs** **Pros (+)** EMDs with audio-visual enabled Vs. EMDs with audio-visual disabled, after 6 months resulted in median adherence of 84% in the EMDs enabled group (10th percentile 54%, 90th percentile 96%), compared with 30% in the EMDs disabled group (8%, 68%) (P<0.0001). EMDs with feedback was compared to EMDs alone. The EMDs with feedback group achieved higher adherence than control (median adherence for the Intervention group was 70% vs. 49% for the control group) (p <0.001). Another study found mean percentage adherence for EMDs with feedback= 79% vs. 57.9% for EMDs without feedback (P< 0.01). **mHealth** **Cons (-)** mHealth (text message reminder with a tip about the value of regular controller use) Vs. control group (receiving only two reminders to sync their sensors). The unadjusted MD: control = 40% vs. mHealth= 34% (P=0.56). Adjusting mean adherence for age and parental education (control=32% vs mHealth=36%, P=0.73). **eHealth** **Cons (-)** A web-based interactive education and monitoring system including education, self-monitoring, and rewards Vs. control (receiving an asthma education manual). Mean change since adherence rate baseline (38%) for intervention 11.2% increase vs. control= 4.4% decrease (P=0.67).
LEE 2021 SYSTEMATIC REVIEW AND META-ANALYSIS SEVEN DATABASES SEARCH FROM INCEPTION UNTIL APRIL 2021 EMD **VS.** USUAL CARE **OUTCOME MEASURES** INHALER ADHERENCE AND CLINICAL OUTCOMES	**EMDs** **Pros (+)** EMDs group was 1.50 times (RR = 1.50, 95% CI 1.19–1.90) more likely to adhere to inhalers VS. control (P<0.001) with medium-to-large effect size (g=0.64). Significant improvement in Children Asthma Control Test (C-ACT) in EMDs group (P=0.02) with a small effect size (g=0.33). **Cons (-)** No significant differences in asthma exacerbation events per year (risk ratio 0.89, 95% CI 0.45–1.75) (P=0.72), or asthma control using ACQ scores (Z −0.91, P=0.36) and ACT scores (Z 0.95, P=0.34).

CHAN 2022 SYSTEMATIC REVIEW AND META-ANALYSIS SEARCH FOR CLINICAL TRIALS FROM THE COCHRANE AIRWAYS TRIALS REGISTER FROM FROM INCEPTION UNTIL JUNE 2020 DIGITAL INTERVENTIONS AMONG CHILDREN AND ADULT ASTHMATIC PATIENTS **VS.** ANY NON-DIGITAL INTERVENTIONS **OUTCOME MEASURES** ADHERENCE ASTHMA CONTROL ASTHMA EXACERBATIONS UNSCHEDULED GP VISITS TIME OFF SCHOOL, WORK DUE TO ASTHMA LUNG FUNCTION QUALITY OF LIFE COST-EFFECTIVENESS ADVERSE EVENTS	**Digital interventions** **Pros (+)** Adherence rate improved by almost 15% with the use of digital technologies Vs. control (MD 14.66%, 95% CI 7.74 to 21.57). Asthma control as change from baseline of various scales improve by a small (SMD 0.31, 95% CI 0.17 to 0.44). Asthma exacerbations (≥1 asthma exacerbation) reduced (risk ratio 0.53, 95% CI 0.32 to 0.91) (P=0.02). Quality of life increased (SMD 0.26 higher, 95% CI 0.07 to 0.45) (P=0.007). **EMDs & mHealth** **Pros (+)** Adherence improved better with EMDs (MD 23% higher, 95% CI 10.84 to 34.16) (P=0.0002) compared to control group. Adherence improved better with short message services (SMS) (MD 12% higher, 95% CI 6.22 to 18.03) (P< 0.0001) compared to control group. No significant subgroup differences for participant age ranging from 2 to 98 years old, for a total of 15,207 participants from 30 studies. **Cons (-)** No significant subgroup differences in FEV1. No data on missed school or workdays, cost-effectiveness, or adverse events.
BERG 1998 A RANDOMIZED, CONTROLLED STUDY SIX-WEEK SELF-MANAGEMENT PROGRAM. 31 ADULTS WITH ASTHMA USING MDI CHRONOLOG **VS.** 24 ADULTS WITH ASTHMA USING ASTHMA DIARY NOTES **OUTCOME MEASURES** ADHERENCE SCORES	**EMDs (MDI Chronolog)** **Pros (+)** Adherence rates measured by MDI Chronolog showed 26% of the experimental group had > 80% adherence rates Vs. 4% in the control group. **Cons (-)** In each arm of intervention, self-reported adherence rates were higher than the monitored adherence rates.