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## **ADHERENCE TO MEDICATION IN CHILDREN AND ADOLESCENTS WITH ASTHMA: METHODS FOR MONITORING AND INTERVENTION**

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## **Structured Abstract**

### **Introduction**

Poor adherence in children with asthma is a major cause of asthma attacks and poor control, leads to large healthcare costs and has been identified as a factor in asthma deaths. However, it is difficult to detect and frequently overlooked leading to inappropriate escalation of asthma treatment. There is a need for cost effective ways to monitor adherence in order to intervene to change this modifiable behaviour.

### **Areas Covered**

Several measurement tools have been developed to assess adherence in adults and children with asthma. The current methods for measuring adherence, both subjective and objective, have several flaws and even the current gold standard, electronic monitoring devices (EMDs), has limitations. This review will outline and critique the adherence monitoring tools and highlight ways in which they have been used for the purpose of intervention.

### **Expert Review**

Although advances have been made in adherence monitoring we still have some way to go in creating the ideal monitoring tool. There are no validated tailored self-monitoring questionnaires for children with asthma and most objective measures, such as prescription refill rate and weighing canisters, over-estimate adherence. Current electronic monitoring devices, although useful, need improved accuracy to ensure that both actuation and inhalation are measured, and the devices need to be affordable for use in routine health care practice.

## 1. Introduction

Currently 1.1 million children in the United Kingdom (UK) are diagnosed with asthma (1). Most children with asthma achieve good disease control with low dose inhaled corticosteroids (ICS), yet some remain poorly controlled despite high intensity treatment. Tragically a significant number of asthma deaths are in young people under the age of 20 (2) and mortality rates for young people in the UK are among the highest in Europe (3). The National Review of Asthma Deaths (NRAD) found that 67% of asthma deaths were avoidable; the most important modifiable factor being patients not taking their prescribed asthma medication in the month and/or year before their death (2).

Medication adherence has been shown to be a problem in several long-term conditions in both adults (diabetes; schizophrenia; heart disease; asthma) and children (HIV, diabetes, juvenile arthritis and asthma) (4). Good adherence in asthma is most commonly defined as taking between 70-80% of prescribed medication (5, 6). Although any cut point for adherence is somewhat arbitrary there is some evidence of clinical effect when adherence falls below certain thresholds. For example, adherence of less than 60% has been found to be associated with significantly higher levels of healthcare utilisation (7). In an observational study, improvements across a range of asthma control measures during a period of electronic monitoring were seen in children with  $\geq 80\%$  adherence, but no improvements were seen in those whose monitored adherence was  $< 60\%$  (6).

Nonadherence in paediatric asthma is a significant issue with reported adherence rates as low as 50% (8). Suboptimal adherence to ICS leads to poor asthma control, severe attacks of wheeze and hospitalisations(9). It is estimated that around 5-10% of asthmatic children have problematic severe asthma (asthma apparently not responding to maximal medications) and these children consume a disproportionate amount of NHS resources (10). Even among this group at least half of patients attending tertiary care paediatric clinics were found to be poorly adherent (11).

There has been a call for change by several key asthma experts. The 2018 Lancet commission recommended that we “develop tests capable of identifying poor adherence and treatment approaches capable of improving adherence”(12). The UK national charity for asthma, Asthma UK, also highlighted the problem of nonadherence in their 2018 research priorities (<https://www.asthma.org.uk/research/strategy/research-priorities/>): “Regardless of how effective asthma treatments are, they will only work if people understand and appreciate their benefits and take them as prescribed... we know that a number of complex barriers exist which unnecessarily limit the level of control most people have over their asthma...”

The ERS/ATS Task Force on severe asthma recommend that nonadherence to treatment should be considered in all difficult to control patients before a label of “severe asthma” can be applied. However, the authors acknowledge that detecting poor adherence can be challenging (13). Similarly, NRAD called for continual monitoring of adherence to ICS.

To achieve these recommendations, we need reliable and affordable ways for healthcare professionals to assess adherence in children with problematic asthma. There are a number of methods for monitoring adherence which will be reviewed. Some are subjective, while others utilise more objective measures. It is important that the correct tool is used to measure adherence in children with asthma. Each of the commonly used measurement tools have strengths and limitations which are summarised in this article alongside research which has used the tools either as an outcome measure or as part of an intervention.

## **2. Adherence Monitoring Tools**

### **2.1 Subjective Monitoring Tools**

#### **2.1.1 Physician Assessment of Adherence**

Physicians have consistently been shown to be unable to accurately identify which of their patients are not adhering to their asthma treatment. A recent study found that health care professionals were extremely poor at detecting nonadherence in their patients when assessing eligibility for advancement to novel biological therapies (14). Both specialist nurses and physicians were able to identify nonadherence in less than half of their patients when compared to objective measures. Adherence was significantly overestimated by nurses in 72% of cases and doctors in 85% of cases (14).

#### **2.1.2 Parental and Child Assessment of Adherence**

Self and parental assessment is often used as a measure of adherence in research studies and in clinical practise as validated assessment tools are generally quick for patients to complete and are viewed as cost effective. However, self and parental reported adherence are often measured using non-validated tools (15-18) . Whether or not a validated tool is used, adherence to ICS is frequently overestimated compared to objective measures (19). There can be a number of reasons for this including wanting to demonstrate behaviour (adherence) that is desired by the medical team. This issue can in some way be addressed by asking empathic questions that acknowledge the likelihood of poor adherence (20).

##### **2.1.2.1 Self-Report Questionnaires**

Self-report questionnaires can be filled in by the parent or the child themselves depending on their development and validation. The most frequently used questionnaires to measure adherence in asthma are the Morisky Scale (21) and the Medicines Adherence's Report Scale - Asthma (MARS-A (22)).

#### 2.1.21.2 The Morisky Scale

The Morisky scale was originally developed as a 4-item questionnaire for hypertension medication adherence with dichotomous yes/ no responses. The scale was found to have good concurrent and predictive validity for objective blood pressure readings at 2 and 5 years. More recently the scale was developed into a more predictive 8-item questionnaire with dichotomous answers except the final answer which was is a five-point Likert scale (23). The Morisky scale has been used in a variety of health conditions including asthma but it has not frequently been used to measure adherence in children with asthma. The studies that have used the Morisky Scale were conducted in mixed populations which included both children and adults (24-29). In 2017 the Morisky scale was developed and validated for use in asthma as an 8 item questionnaire (Morisky Medication Adherence Scale, MMAS-8) (30) in patients over 12 years old. The questionnaire was tested in a Slovenian population and correlated well with asthma control and quality of life. However, it has not been validated using objective measures of adherence.

#### 2.1.2.1.3 The Medication Adherence Report Scale (MARS)

The Medication Adherence Report Scale (MARS) was originally developed and validated in multiple disease populations including asthma (31). The MARS consists of 9 items which are all scored on a 5-point Likert scale and it has been adapted for the asthmatic population specifically to address adherence to ICS. The MARS-A, a 10-item scale was validated in adult patients with asthma and has been found, in research studies, to be only moderately correlated with electronic monitoring data ( $r = 0.42$ ,  $P = 0.001$ ) (22). However, in children it is often the parents who complete the questionnaire on behalf of the child (32, 33) and both the MARS-A and MARS-5, a shortened version, have been found to be inaccurate in children when administered in clinical practice and compared to EMD data (6, 34).

## 2.2 Objective Monitoring tools



### 2.2.1 Prescription Data

Prescription data is an objective measure which is often used as a proxy for adherence (36, 37). It describes how often the patient (or parent of a patient) is prescribed a prescription, usually for ICS or other maintenance therapy, and presented as a percentage of the expected number of prescriptions over a given time period (usually one year). Although objective, prescription data only give an indication of complete non-adherence; if no prescriptions are collected then no medication can be taken but collecting a prescription script is not the same as collecting the medication from the pharmacy or inhaling the medication. Prescription data are relatively easy to obtain, particularly by the primary care physician and this is often used clinically as a proxy for nonadherence.

Prescription refill rate (PRR) describes the amount of medication actually collected from a pharmacy. Although this gives a little more information than simple prescription data it also does not allow for the unknown factor of whether patients actually take the medication or just store them until they go out of date (38). Furthermore, in areas where prescriptions are free for children, parents may collect medications ostensibly for their child, but in reality, for another adult, to take advantage of the cost savings. Despite the limitations of PRR it can provide useful insights into medication use and is a popular adherence outcome for research studies targeting adherence and has been used in many intervention studies in children with asthma (37, 39, 40). Despite the limitations of PRR it can also provide useful information on salbutamol use. Collection of 12 or more salbutamol inhalers was highlighted as a risk factor for asthma death by NRAD (2). This equates to >6puffs per day, every day, indicative of very poor asthma control and suggestive of discordance between preventer and reliever use.

### 2.2.2 Weighing Inhaler Canisters

Inhaler canisters returned to the clinician/researcher can be weighed using a digital scale to calculate the number of doses used. This method is costly as it requires a digital scale to be accessible. Again assumptions that have to be made may be incorrect and the results misleading, particularly if the patient has engaged in dose dumping, where a patient actuates the inhaler multiple times to discharge the drug in an attempt to appear adherent, just before bringing the inhalers back or if the inhaler has been used by someone else (41). Canister weight is used more frequently in trials than in the clinical setting and it has been used to measure adherence in an RCT in children with asthma prescribed ICS (42). Weicha et al. (42) used canister weight in comparison to self-report adherence from both children with asthma and their parents and found that the objective versus subjective measures were vastly different with the objective measures (canister weight and DOSER CT™ being lower than the

subjective measures). This objective measurement allows researchers and clinicians to calculate how much of the medication has been taken (actuated not necessarily inhaled) although it does not have a mechanism to adjust for dose dumping.

### 2.2.3 Dose Counters

Dose counters indicate to the patient how many doses remain in their inhaler. The counter decreases as doses are taken or the inhaler is actuated and is embedded in the inhaler device. Clinicians or researchers may use this as an indication of adherence as it is easily accessible. However, as with weighing inhaler canisters the dose counter can be manipulated by dose dumping as the investigator has no indication of when the doses were taken or even if they were inhaled.

### 2.2.4 Directly Observed Therapy

Directly observed therapy (DOT) had long been used for diseases such as tuberculosis to ensure compliance with the whole treatment course. It can also be utilised in asthma to ensure a child takes their inhalers regularly, usually observed by a member of school staff, local pharmacy or nursing team. A recent pilot study has utilised a mobile device platform for remote direct observation of inhaler use and technique (43). Children are filmed using their device and then the video is uploaded via an App and reviewed by a specialist asthma nurse to assess inhaler technique. Mobile directly observed therapy (MDOT) is more flexible and convenient for children and their families than standard DOT and also has the advantage that inhaler technique is observed by someone with appropriate expertise. However, failure to upload a video does not mean that a child has not used their inhaler and is therefore not a measure of adherence per se. Furthermore, it is time intensive for families and nursing staff and requires children and their carers to not only remember to take the inhaler but to film it as well. There are also issues around data security and confidentiality.

### 2.2.5 Nurse Home Visits

Nurse led home visits can provide useful insights into adherence and provide information to complement self-report and prescription data. At the time of a home visit the location of all prescribed medications can be checked including whether they are easily accessible and if medications are present, whether they are within their use by date. Stockpiling of medications demonstrates that although inhalers are collected they are not being taken (11).

## 2.3 Electronic Monitoring Devices

Electronic Monitoring Devices (EMDs) for asthma inhalers have been the focus of adherence research over the last 15 years. With advancements in technology improving year on year several types of devices have been developed, all with differing capabilities and prices. The current gold standard for measuring adherence is the use of EMDS such as the Smartinhaler™ (44). These EMDs measure when and how often patients activate their inhaler but currently not whether they are inhaling correctly. EMDs also do not provide information on why patients are nonadherent and they are currently not affordable for all clinical care settings.

### 2.3.1 DOSER CT™

One of the first electronic monitoring devices for metered dose inhalers was the DOSER CT™ (45). The DOSER CT™ can be used with MDIs to count the number of doses used within a day up to 30 days (based on battery life). The DOSER CT™ uses a microchip and displays the amount of doses taken on the screen although this is a simple sum of the doses taken as opposed to the time and date of each dose. The DOSER CT™ is the cheapest EMD for ICS as it uses older technology than some of the newer EMDs but its key downfall is its inability to adjust for potential dose dumping. The DOSER CT™ has been used in a recent randomised control trial intervention based in America in children with asthma (42). The trial assessed changes in adherence between patients in the control group compared to those in the intervention group (a web-based self-management website named BostonBreathes). As the study was underpowered it did not find a significant difference in the DOSER CT™ adherence scores between groups however a post hoc analysis looking at those with low baseline adherence did show a significant improvement in those randomised to the intervention group (19).

### 2.3.2 SmartInhalers™

SmartInhaler™ (Adherium, New Zealand) are currently considered the gold standard in clinically available tools, for objectively and accurately recording adherence data in asthmatic patients (46). They are fitted to the child's usual inhaler and contain a microchip which collects data on when and how often an inhaler is actuated. The calculation of adherence from this device is not affected by dose dumping as it records the exact time, day and number of doses actuated so that the clinician/researcher can see if dose dumping has occurred and disregard the over-use of medication (if it is not relevant to their research). The device can be fitted to many different types of inhalers and is easy for patients to transfer the device to a new inhaler when a prescription is renewed. Newer versions of the Smartinhaler are Bluetooth enabled. Children or their parents can download an App enabling them to monitor their own adherence, or health professionals can utilise this functionality to remotely monitor adherence and intervene rather than waiting for the device to be returned to clinic.

Although this can be beneficial it raises a number of issues: the time and resources needed for clinical staff to regularly monitor adherence and contact families; establishing who is responsible for ensuring a child's adherence; and maintaining engagement and trust with the family rather than featuring in their lives as a "Big Brother" presence (47).

As well as monitoring adherence, a number of studies have investigated their utility as an adherence intervention (48, 49). This is certainly plausible: one would expect that children would be more likely to take their inhalers if they know they are being monitored and the reminder function on the Smartinhalers can help those whose poor adherence is due to forgetfulness and poor routine. Three paediatric randomised controlled trials of EMDs, demonstrated impressive differences in monitored adherence between the control and intervention arms (30% versus 85%; 49% versus 70% and 57.9% versus 79% respectively) (48-50). Chan et al. (48) noted significant improvement in a secondary outcome, asthma control scores, in the intervention group during the six month monitoring period and Morton et al. (49) noted a significant difference in asthma exacerbations over a 12 month period. However, interestingly significant difference between groups were not found for the three studies' primary outcomes (time off school, change in ACQ score and FEV<sub>1</sub>% predicted respectively (48-50). This may in part be due to the fact that Smartinhalers measure actuation and not inhalation. It is possible that those with good adherence were using their devices incorrectly or deliberately manipulating them. A recent study demonstrated that real adherence is far less than actuations counted (51). Furthermore, adherence remained suboptimal (<80%) in a significant proportion of those monitored, suggesting that monitoring alone is insufficient as a sustained intervention. None-the-less, important insights can be gained from the use of these devices. One study demonstrated that a period of monitoring is essential in determining management in those with problematic severe asthma (poor control despite prescription of high dose asthma treatment) (6). The study identified four groups: those with genuine severe asthma i.e. persistent poor control despite monitored good adherence who are candidates for a step up in treatment including addition of expensive biologics; those with good adherence whose control improved during the monitoring period (likely as a result of improved adherence), they require support to maintain adherence; those with poor adherence but improved control who require an intervention to improve adherence but are likely over-treated; and those with poor adherence and poor control for whom an adherence intervention is needed. Analysis of the adherence patterns can also be used as the basis for an honest and open discussion about adherence and as the basis for planning an appropriate adherence intervention (52, 53).

### 2.3.3 Propeller Health (previously named Asthmapolis Device)

The Propeller Health electronic monitoring device attaches to the top of a pMDI inhaler canister or on the side of a DPI Diskus™ (Accuhaler) and measures, through GPS, both the location and the time and date of each inhaler actuation. The adherence data from the device can be downloaded using a USB cable or Bluetooth to a specifically designed smartphone application. The battery is rechargeable and the patient can fit the device onto any repeat prescription of the same inhaler. Propeller Health, which is FDA approved, has been used to measure both short acting beta agonist (SABA) (54) and ICS (55). Propeller Health has recently been used to measure SABA use in a large RCT (56) however to date no RCT has been conducted in ICS use. SABA use is likely to be investigated more frequently in the future as an indicator of poor adherence to ICS as high SABA use often correlates with low ICS use and vice versa. Propeller health devices are currently expensive costing approximately \$300 per device.

#### 2.3.4 Inhaler Compliance Assessment (INCA) device

The Inhaler Compliance Assessment (INCA) device measures adherence by recording the time and date of the actuation but importantly also contains acoustic sensors which can detect inhalation (57, 58). This has clear advantages over the currently commercially available Smartinhalers; however, it is only clinically available for the Diskus™ (Accuhaler) inhaler, a dry powder inhaler which is not suitable for younger children and has only been evaluated in adults. Current work is ongoing to make this technology adaptable to pMDIs for use in COPD and asthma within a clinical setting (59).

Sulaiman et al. (60) have used the INCA to develop an algorithm to measure adherence over time (an area under the curve(AUC) measure), which takes into account the time between doses as well as the inhaler technique, using acoustic sensors. Measuring actuation alone significantly overestimates adherence. Furthermore, only the AUC method was significantly associated with positive changes in asthma quality of life, reliever use, and peak expiratory flow recordings over 3 months.

The device has recently been tested in a randomised controlled trial in adults with severe uncontrolled asthma (58). Participants were randomised to an intensive education programme including inhaler technique or biofeedback based on data from the INCA device over a three-month period. Those in the biofeedback group had significantly higher actual adherence (both actuation and correct technique) in the third month of the intervention than the intensive education group (73% versus 63%; 95% CI 2.8%-17.6%;  $p=0.02$ ). Furthermore, the device enabled the identification of clinically meaningful groups, including those who remained “difficult to manage” (uncontrolled with poor adherence despite monitoring). Similar groups were described previously in the Jochmann study; however, in that study the authors were unable to determine if those participants with poor control despite documented good adherence had poor inhaler technique or were refractory to treatment. This device certainly shows promise. Adapting this technology for other inhaler devices would enable

testing in a greater range of patient groups, including children. Further work is needed to see if a period of monitoring with biofeedback can lead to sustained improvements in inhaler technique.

## 2.4 Integrating digital technologies

The increasing use of technology to monitor adherence affords the opportunity to integrate monitoring with digital adherence interventions. As discussed above a number of EMD devices have utilised reminder functions built into the device (48, 49). However, an alarming device will only be effective if it is in close proximity to its user. A number of studies have looked at other ways of providing prompts. The almost ubiquitous presence of a personal Smartphone suggests a much more effective conduit for delivery of reminders. Short messaging service (SMS) / text or phone messages have been shown to have a positive impact on adherence (61). Propeller health devices have also been used in conjunction with text message reminders with children with asthma. This pilot study is registered on [clinicaltrials.org](http://clinicaltrials.org) but has yet to publish results (ref: NCT02615743, (55)). Within the current literature objective measures of adherence are generally lacking in text message studies and there has been little impact demonstrated on clinical control. In one adolescent study only 37% of participants offered SMS medication reminders successfully adopted this feature (62). However, such interventions need to be tailored to the target population and text messages and telephone calls are not the standard means of communication for most young people. Newer versions of EMDs have an associated App enabling the reminder to be delivered via a mobile device. Such Apps also afford the user the opportunity to monitor their own adherence, providing support for directed self-management. Whether evidence of benefit can be demonstrated before technology has again moved on remains to be seen.

## 2.5 Biomarkers of adherence

### 2.5.1 Drug levels

Measurement of theophylline levels is usually undertaken to ensure the dose is in the therapeutic range; however very low or undetectable levels measured in either serum or saliva indicate poor compliance (63). Interpretation of these levels depends on knowing when the drug was reported or scheduled to have been taken and are unreliable if taken more than 12 hours after administration of a slow release tablet or 2 hours after immediate release preparations. For those on maintenance oral steroids serum prednisolone levels can be measured (64). This assay is only valid if measured within 6 hours of the dose. A suppressed random cortisol level would also be expected if prednisolone has been taken regularly. Prednisolone assays are available only in specialist centres and timing can be

difficult particularly for children prescribed alternate day prednisolone, who always seem to attend clinic on the day they are not scheduled to take the dose! Whilst drug levels can be useful, only a very small number of children are prescribed theophylline or maintenance prednisolone. It is possible to measure inhaled steroid metabolites in blood and urine (65), however at present these assays are generally only available in research settings or doping labs.

#### 2.4.2 Exhaled nitric oxide

Fraction of exhaled nitric oxide (FENO) is an indirect measure of eosinophilic airway inflammation and usually falls in response to inhaled steroids. FENO at the end of a period of monitoring with an EMD was found to have the best correlation with adherence and a significant fall in FENO was observed in those with good ( $\geq 80\%$ ) and moderate (60-79%) adherence over the monitoring period (6). FENO suppression has been shown to be useful in identifying nonadherence in adult patient with difficult asthma (DA) both in the context of research and clinically. McNicholl et al. (66) explored this in patients with FENO of ( $>45\text{ppb}$ ) and patients who collected 80% or more versus less than 50% of their ICS prescriptions. They found FENO suppression to be a useful objective measure after directly observed therapy to detect poor adherence in difficult asthma. FENO is increasingly available in clinical care and could be combined with either DOT or EMD monitoring to identify those with previous poor adherence. However, it may be less useful in children. In the Jochmann study (6) 35% of the paediatric cohort had FENO levels of  $<25\text{ppb}$  at enrolment and therefore FENO suppression cannot be used in these patients. Furthermore, FENO did not distinguish those with poor control and poor adherence and those with poor control and good adherence.

The key features of monitoring tools are summarised in Table 1.

**Table 1: Pros and Cons of the key adherence monitoring measurement tools**

Type of Tool	Development Year	Pros	Cons	Published data on reliability
<b>2.1</b>				
<b>Subjective</b>				
2.1.2.1.2 Morisky Scale	MMAS- 1986 MMAS-8- 2017	<ul style="list-style-type: none"> <li>• Short and easy to administer</li> <li>• Inexpensive</li> </ul>	<ul style="list-style-type: none"> <li>• Originally developed in hypertension</li> <li>• Not used frequently in paediatric asthma research</li> </ul>	<ul style="list-style-type: none"> <li>• Yes (21, 23)</li> </ul>
2.1.2.1.3 Medicines Adherence Report Scale (MARS – A and MARS-5)	MARS MARS-5- 2002 MARS-A- 2009	<ul style="list-style-type: none"> <li>• Short and easy to administer</li> <li>• Inexpensive</li> <li>• Correlates to electronic monitor data in the adult validation study</li> <li>•</li> </ul>	<ul style="list-style-type: none"> <li>• Self-report generally over-estimates adherence in children in clinical settings</li> </ul>	<ul style="list-style-type: none"> <li>• Yes (22)</li> </ul>
<b>2.2</b>				
<b>Objective</b>				
2.2.4 Mobile Directly Observed Therapy	2018	<ul style="list-style-type: none"> <li>• Inhaler technique can be checked in addition to adherence</li> <li>• MDOT reduces the travel burden for traditional DOT at the hospital or a community location</li> </ul>	<ul style="list-style-type: none"> <li>• Patients may take their inhaler without uploading a video</li> <li>• Reviewing videos is time consuming for the clinicians (expensive)</li> <li>• Uploading the video relies on an internet connection</li> </ul>	<ul style="list-style-type: none"> <li>• Yes (43)</li> </ul>
<b>2.3</b>				
<b>Electronic Monitoring Devices</b>				
2.3.1 Doser CT™	1998	<ul style="list-style-type: none"> <li>• Most inexpensive of the electronic devices</li> <li>• Records the number of actuations</li> </ul>	<ul style="list-style-type: none"> <li>• Does not record the time and date of each actuation- open to dose dumping</li> <li>• Memory is only 30 days long</li> </ul>	<ul style="list-style-type: none"> <li>• Yes (45)</li> </ul>
2.3.2 SmartInhalers™	2006	<ul style="list-style-type: none"> <li>• Measures when and how often ICS is taken- avoids dose dumping</li> <li>• Can be put onto different types on inhalers by the patient/parent</li> <li>• It is commercially available</li> <li>• Can have a reminder alarm enabled</li> </ul>	<ul style="list-style-type: none"> <li>• Expensive</li> <li>• Can be manipulated as actuation not inhalation measured</li> <li>• It does not measure inhalation</li> <li>• Bluetooth enabled</li> </ul>	<ul style="list-style-type: none"> <li>• Yes (46)</li> </ul>



		<ul style="list-style-type: none"> <li>• Rechargeable</li> <li>• Bluetooth enabled link to a mobile app</li> </ul>		
2.3.3 Propeller Health	2018	<ul style="list-style-type: none"> <li>• GPS enabled</li> <li>• Measures when and how often ICS is taken- avoids dose dumping</li> <li>• It has a light which tells the user when in needs charging, when a dose is taken and when it is plugged into the USB cable</li> <li>• It is Bluetooth enabled and has its own app</li> </ul>	<ul style="list-style-type: none"> <li>• The most expensive device</li> <li>• It is not currently available for routine clinical use Not commercially available for clinical use</li> <li>• It does not measure inhalation</li> </ul>	<ul style="list-style-type: none"> <li>• Yes (54, 55)</li> </ul>
2.3.4 Inhaler Compliance Assessment (INCA)	2013	<ul style="list-style-type: none"> <li>• Measures how, when and how often a dose is taken- avoids dose dumping</li> <li>• Measures inhalation technique</li> </ul>	<ul style="list-style-type: none"> <li>• Not commercially available for clinical use</li> <li>• Only available for DPIs (pMDI in development)</li> <li>• It is not Bluetooth enabled and does not have an accompanying app</li> <li>• Only validated in adults with an effect over a three month period</li> </ul>	<ul style="list-style-type: none"> <li>• Yes (57, 58)</li> </ul>

### 3. Conclusion

No single self-report adherence questionnaire has been developed and validated with children with asthma and therefore they have shown limited clinical use. Although other clinical tools such as prescription data can be a useful and low cost way to assessment tool they are likely to overestimate adherence. EMDs are currently seen as the gold standard for measurement of adherence in asthma. However, current EMDs have key limitations including the lack of measurement of inhalation and the high cost. The development of the next generation of EMDs which can assess inhalation and inhaler technique is exciting and to be welcomed.

### 4. Expert commentary

Optimising adherence to medications is a key challenge in asthma management. Over the past 15 years the development, and increasing use, of electronic monitoring devices have enabled a more accurate assessment of adherence – an essential starting point in identifying and improving poor adherence. However, these devices are not a panacea. They do not capture the patient’s “usual” adherence as the process of monitoring leads to improved adherence in many. Conversely, they do

not appear to be a sufficient intervention in themselves to lead to sustained improvements in asthma control: adherence decreases the longer the monitoring period and crucially, in all but the INCA device, they monitor actuation and not inhalation. None-the-less they can provide valuable data both for the patient and the healthcare provider. Firstly, asthma control can be interpreted in the context of known adherence; secondly the combination of adherence data and changes in asthma control during a period of monitoring can be used as the basis of a concordance interview and to identify an appropriate adherence intervention; and finally the reminder function and connectivity with an App which records usage may be helpful for some patients as a tool to improve adherence.

The current costs and availability of EMDs limits their use and they are not part of mainstream care in most territories. Given the huge costs of asthma management it is possible that the use of these devices could lead to financial savings making them attractive to providers/ payers, and therefore a health economic analysis of their use would be most welcome. In the meantime, other forms of adherence monitoring such as prescription refill rate and empathic questioning have their role, provided the limitations, as discussed in this article, are recognised.

The further development of novel digital platforms is a fast-moving field. EMDs which include a measure of inhalation (either utilising acoustic or flow sensors or video capture) offer greater potential to improve asthma control by addressing practical barriers (i.e. inhaler technique). Further studies are needed to assess whether they do offer benefit over currently available devices. There is a risk that the greater the functionality, the greater the cost and likelihood of device failure. Improving reliability and driving down costs of current devices may yield greater benefit on a population level whereas more sophisticated devices may have greater utility for the individual. The differential pace of technology development compared to clinical trials is a challenge for those working in this area and a balance must be struck between innovation and evidence of benefit.

Recognising poor adherence is an important step in asthma management; however, it is of little use unless it leads to meaningful engagement with the patient. Knowing whether a patient is adherent or not does not uncover the myriad reasons for poor adherence nor does it automatically lead to improved adherence. Non-judgemental patient doctor communication based on objective adherence data is vital to target adherence behaviour effectively. Combining EMDs with a simple questionnaire tool to profile adherence beliefs in individuals could help to identify key areas for discussion between patients and healthcare providers and to personalise adherence interventions.

The importance of adherence in asthma care is well established. Decreasing costs and improved usability of EMDs offers the prospect of adherence monitoring becoming part of mainstream care. It is possible that in the near future all inhalers could contain some sort of in-built monitoring device. The technological challenges are relatively easy to address; implementing behaviour change on the part of the patient and the healthcare provider is a mountain yet to be climbed.

## **5. Five-year view**

We expect that within five years a range of electronic monitoring devices will be available for clinical use to measure both inhaler technique and medication adherence. Using these devices at scale should lead to reduced costs enabling them to be part of mainstream asthma care. We hope that these devices are embraced and used by clinicians to better understand, discuss and influence adherence behaviour in people with asthma. We envisage that they will become a key element of directed self-management and will be integrated with other digital technologies to improve asthma monitoring.

### Key issues

- Self-report adherence questionnaires have not been utilised successfully in clinical studies in children although to date there are no questionnaires which have been developed for, and validated in paediatric populations
- There are a number of objective measures which can be utilised, particularly in a specialist setting, including nurse-led home visits; biomarkers such as FENO suppression monitoring and prescription data but each have limitations
- Within the last 15 years Electronic Monitoring Devices (EMDs) have been the focus for monitoring adherence, however each of these too have their limitations: availability of devices; cost; the ability of the patient to manipulate the data (i.e. by dose dumping or by actuating without inhaling); accuracy of inhaler technique is not always known; and EMDs are not available for all types of inhalers
- Next generation EMDS include the ability to measure inhalation and potentially inhaler technique
- At present there is little evidence to suggest that EMDs are a sustainable adherence intervention
- Recognition of poor adherence is the starting point for non-judgmental discussions around inhaler use and the basis of identifying an appropriate intervention

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## References

Papers of special note have been highlighted as either of interest (\*) or of considerable interest (\*\*) to readers.

1. UK A. Time to Take Action 2014 Available from: <https://www.asthma.org.uk/globalassets/campaigns/compare-your-care-2014.pdf>.
2. Levy ML. National Review of Asthma Deaths (NRAD). *Br J Gen Pract.* 2014;64:564
3. Wolfe I, Thompson M, Gill P, et al. Health services for children in western Europe. *Lancet.* 2013;381:1224-34
4. Santer M, Ring N, Yardley L, et al. Treatment non-adherence in pediatric long-term medical conditions: systematic review and synthesis of qualitative studies of caregivers' views. *BMC Pediatr.* 2014;14:63
5. Santos Pde M, D'Oliveira A, Jr., Noblat Lde A, et al. Predictors of adherence to treatment in patients with severe asthma treated at a referral center in Bahia, Brazil. *J Bras Pneumol.* 2008;34:995-1002
6. Jochmann A, Artusio L, Jamalzadeh A, et al. Electronic monitoring of adherence to inhaled corticosteroids: an essential tool in identifying severe asthma in children. *The European respiratory journal.* 2017;50
7. McNally KA, Rohan J, Schluchter M, et al. Adherence to combined montelukast and fluticasone treatment in economically disadvantaged african american youth with asthma. *Journal of Asthma.* 2009;46:921-7
8. Morton RW, Everard ML, Elphick HE. Adherence in childhood asthma: the elephant in the room. *Archives of Disease in Childhood.* 2014;99:949-53
9. Williams LK, Peterson EL, Wells K, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. *J Allergy Clin Immunol.* 2011;128:1185-91 e2
10. Bush A, Hedlin G, Carlsen KH, et al. Severe childhood asthma: a common international approach? *Lancet.* 2008;372:1019-21
11. Bracken M, Fleming L, Hall P, et al.. The importance of nurse-led home visits in the assessment of children with problematic asthma. *Archives of Disease in Childhood.* 2009;94:780-4
12. Pavord ID, Beasley R, Agusti A, et al. After asthma: redefining airways diseases. *Lancet.* 2018;391:350-400
13. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *The European respiratory journal.* 2014;43:343-73
14. Lee J, Tay TR, Radhakrishna N, et al. Nonadherence in the era of severe asthma biologics and thermoplasty. *The European respiratory journal.* 2018;51
15. Teach SJ, Crain EF, Quint DM, H, et al. Improved asthma outcomes in a high-morbidity pediatric population: results of an emergency department-based randomized clinical trial. *Archives of Pediatrics & Adolescent Medicine.* 2006;160:535-41
16. Mosnaim G, Li H, Martin M, et al. The Impact of Peer Support and mp3 Messaging on Adherence to Inhaled Corticosteroids in Minority Adolescents with Asthma: A Randomized, Controlled Trial. *Journal of Allergy and Clinical Immunology: In Practice.* 2013;1:485-93
17. van Es SM, Nagelkerke AF, Colland VT, et al. An intervention programme using the ASE-model aimed at enhancing adherence in adolescents with asthma. *Patient Education and Counseling.* 2001;44:193-203
18. Stergachis A, Gardner JS, Anderson MT, et al. Improving pediatric asthma outcomes in the community setting: does pharmaceutical care make a difference? *Journal of the American Pharmaceutical Association (Washington,DC : 1996).* 2002;42:743-52
19. Bender B, Wamboldt F, O'conner S, et al. Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. *Annals of Allergy, Asthma and Immunology.* 2000;85:416-21

20. E.D. Bateman, S.S. Hurd, P.J. Barnes, et al. Global strategy for asthma management and prevention: GINA executive summary. *European Respiratory Journal*. 2018;51
21. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Medical care*. 1986;24:67-74
22. Cohen JL, Mann DM, Wisnivesky JP, et al. Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. *Ann Allergy Asthma Immunol*. 2009;103:325-31
23. Morisky DE, Ang A, Krousel-Wood M, et al. Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens (Greenwich)*. 2008;10:348-54
24. Ngahane BH, Pefura-Yone EW, Mama M, et al. Evaluation of factors affecting adherence to asthma controller therapy in chest clinics in a sub-Saharan African setting: a cross-sectional study. *African health sciences*. 2016;16:194-200
25. Ivanova JI, Birnbaum HG, Hsieh M, et al. Adherence to inhaled corticosteroid use and local adverse events in persistent asthma. *The American journal of managed care*. 2008;14:801-9
26. Guenette L, Breton MC, Gregoire JP, et al. Effectiveness of an asthma integrated care program on asthma control and adherence to inhaled corticosteroids. *The Journal of asthma : official journal of the Association for the Care of Asthma*. 2015;52:638-45
27. Giraud V, Allaert FA. Improved asthma control with breath-actuated pressurized metered dose inhaler (pMDI): the SYSTER survey. *Eur Rev Med Pharmacol Sci*. 2009;13:323-30
28. Morisky DE, Kominski GF, Afifi AA, et al. The effects of a disease management program on self-reported health behaviors and health outcomes: evidence from the "Florida: a healthy state (FAHS)" Medicaid program. *Health Educ Behav*. 2009;36:505-17
29. Davis J, Trudo. F, Siddall. J, et al. Burden of asthma among patients adherent to ICS/LABA: A real-world study. *Journal of Asthma*. 2018:1-9
30. Janezic A, Locatelli I, Kos M. Criterion validity of 8-item Morisky Medication Adherence Scale in patients with asthma. *PloS one*. 2017;12:e0187835
31. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. *Journal of Psychology & Health*. 1999;14:1-24
32. Klok T, Kaptein AA, Duiverman EJ, et al. High inhaled corticosteroids adherence in childhood asthma: the role of medication beliefs. *European Respiratory Journal*. 2012;40:1149-55
33. Menard S, Jbilou J, Lauzier S. Family caregivers' reported nonadherence to the controller medication of asthma in children in Casablanca (Morocco): Extent and associated factors. *The Journal of asthma : official journal of the Association for the Care of Asthma*. 2018:1-11
34. Garcia-Marcos PW, Brand PLP, Kaptein AA, et al. Is the MARS questionnaire a reliable measure of medication adherence in childhood asthma? *Journal of Asthma*. 2016;53:1085-9
35. Bracken M, Fleming L, Hall P, et al. The importance of nurse-led home visits in the assessment of children with problematic asthma. *Arch Dis Child*. 2009;94:780-4
36. Horspool MJ, Julious SA, Boote J, et al. Preventing and lessening exacerbations of asthma in school-age children associated with a new term (PLEASANT): study protocol for a cluster randomised control trial. *Trials [Electronic Resource]*. 2013;14:297
37. Garrett J, Fenwick JM, Taylor G, et al. Prospective controlled evaluation of the effect of a community based asthma education centre in a multiracial working class neighbourhood. *Thorax*. 1994;49:976-83
38. Hazell B, Robson R. Pharmaceutical waste reduction in the NHS. 2015. Report No.: Version 1.
39. Julious S, Horspool M, Davis S, et al. PLEASANT: Preventing and lessening exacerbations of Asthma in school-age children associated with a new term-a cluster randomised controlled trial and economic evaluation. *Health Technology Assessment*. 2016;20:1-154
40. Gustafson D, Wise M, Bhattacharya A, et al. The effects of combining Web-based eHealth with telephone nurse case management for pediatric asthma control: a randomized controlled trial. *Journal of medical Internet research*. 2012;14:e101

41. Rand CS, Wise RA. Measuring adherence to asthma medication regimens. *Am J Respir Crit Care Med.* 1994;149:S69-76; discussion S7-8
42. Wiecha JM, Adams WG, Rybin D, et al. Evaluation of a web-based asthma self-management system: a randomised controlled pilot trial. *BMC Pulm Med.* 2015;15:17
43. Shields MD, ALQahtani F, Rivey MP, et al. Mobile direct observation of therapy (MDOT) - A rapid systematic review and pilot study in children with asthma. *PloS one.* 2018;13:e0190031
44. Chan AH, Harrison J, Black PN, et al. Using electronic monitoring devices to measure inhaler adherence: a practical guide for clinicians. *J Allergy Clin Immunol Pract.* 2015;3:335-49 e1-5
45. Simmons MS, Nides MA, Klerup EC, et al. Validation of the Doser, a new device for monitoring metered-dose inhaler use. *J Allergy Clin Immunol.* 1998;102:409-13
46. Vrijens B, Dima AL, Van Ganse E, et al. What We Mean When We Talk About Adherence in Respiratory Medicine. *Journal of Allergy and Clinical Immunology: In Practice.* 2016;4:802-12
47. Stewart AC, Gannon KN, Beresford F, et al. Adolescent and caregivers' experiences of electronic adherence assessment in paediatric problematic severe asthma. *J Child Health Care.* 2018:1367493517753082
48. Chan AH, Stewart AW, Harrison J, et al. The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial. *The Lancet Respiratory medicine.* 2015;3:210-9
49. Morton RW, Elphick HE, Rigby AS, et al. STAAR: a randomised controlled trial of electronic adherence monitoring with reminder alarms and feedback to improve clinical outcomes for children with asthma. *Thorax.* 2017;72:347-54
50. Burgess SW, Sly PD, Devadason SG. Providing Feedback on Adherence Increases Use of Preventive Medication by Asthmatic Children. *Journal of Asthma.* 2010;47:198-201
51. Sulaiman I, Seheult J, MacHale E, et al. A method to calculate adherence to inhaled therapy that reflects the changes in clinical features of asthma. *Ann Am Thorac Soc Journal Translated Name Annals of the American Thoracic Society.* 2016;13:1894-903
52. Pearce C.J, Jochmann A, Bush A, et al. Patterns of nonadherence in children with severe asthma. *European Respiratory Society; 2016; London: European Respiratory Journal.*
53. Pearce C.J., Fleming L, Chan A., et al. "What's a preventer and why do I need it anyway?" A qualitative study in young people with asthma using SmartInhalers™. *Asthma UK Centre for Applied Research Annual General Meeting; 2018; Bristol.*
54. Barrett MA, Humblet O, Marcus JE, et al. Effect of a mobile health, sensor-driven asthma management platform on asthma control. *Ann Allergy Asthma Immunol.* 2017;119:415-21 e1
55. Adams SA, Leach MC, Feudtner C, et al. Automated Adherence Reminders for High Risk Children With Asthma: A Research Protocol. *JMIR Res Protoc.* 2017;6:e48
56. Merchant R, Inamdar R, Quade RC. Effectiveness of Population Health Management Using the Propeller Health Asthma Platform: A Randomized Clinical Trial. *Journal of Allergy and Clinical Immunology: In Practice.* 2016;4:455-63
57. Holmes MS, D'Arcy S, Costello RW, et al. Acoustic Analysis of Inhaler Sounds From Community-Dwelling Asthmatic Patients for Automatic Assessment of Adherence. *IEEE J Transl Eng Health Med.* 2014;2:2700210
58. Sulaiman I, Greene G, MacHale E, et al. A randomised clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma. *European Respiratory Journal.* 2018;51
59. Taylor TE, Zigel Y, Egan C, et al. Objective Assessment of Patient Inhaler User Technique Using an Audio-Based Classification Approach. *Scientific reports.* 2018;8:2164
60. Sulaiman I, Seheult J, MacHale E, et al. A Method to Calculate Adherence to Inhaled Therapy that Reflects the Changes in Clinical Features of Asthma. *Ann Am Thorac Soc.* 2016;13:1894-903
61. Tran N, Coffman JM, Sumino K, et al. Patient reminder systems and asthma medication adherence: a systematic review. *The Journal of asthma : official journal of the Association for the Care of Asthma.* 2014;51:536-43

62. Johnson KB, Patterson BL, Ho YX, et al. The feasibility of text reminders to improve medication adherence in adolescents with asthma. *J Am Med Inform Assoc.* 2016;23:449-55
63. Eney R.D, Goldstein E.O. Compliance of Chronic Asthmatics With Oral Administration of Theophylline as Measured by Serum and Salivary Levels. *Paediatrics.* 1976;57:513-7
64. Robinson DS, Campbell DA, Durham SR, et al. Systematic assessment of difficult-to-treat asthma. *The European respiratory journal.* 2003;22:478-83
65. George K.E, Ryan D.M, Keevil B, et al. A pilot study to investigate the use of serum inhaled corticosteroid concentration as a potential marker of treatment adherence in severe asthma. *Journal of Clinical Immunology* 2017;139:1037-9
66. McNicholl DM, Stevenson M, McGarvey LP, et al. The utility of fractional exhaled nitric oxide suppression in the identification of nonadherence in difficult asthma. *Am J Respir Crit Care Med.* 2012;186:1102-8