

Use of Metered-Dose Inhaler Electronic Monitoring in a Real-World Asthma Randomized Controlled Trial

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What is already known about this topic? Electronic monitoring of inhaled asthma medications can provide data on adherence and patterns of use. The Smartinhaler Tracker is an electronic monitor for metered-dose inhalers (MDIs) that records the date, time, and number of actuations.

What does this article add to our knowledge? Implementation of pre- and within-study quality control processes can help to safeguard data acquisition. The Tracker is a reliable electronic monitor of MDI use by asthma patients in a real-world randomized controlled trial.

How does this study impact current management guidelines? Use of extensive monitor checking protocols can help to identify malfunctioning monitors and reduce data loss. Validated and reliable electronic monitors are the gold standard for measuring patterns of medication use.

BACKGROUND: Electronic monitoring of inhaled asthma medications is one method to measure medication adherence and patterns of use. Information on the performance of monitors in a randomized controlled trial allows researchers and clinicians to understand their utility and limitations. The Smartinhaler Tracker is an electronic monitor for metered-dose inhalers (MDIs) that records the date, time, and number of actuations.

OBJECTIVE: To determine the performance of the Smartinhaler monitors used in a 24-week randomized controlled trial of 303 patients with asthma in a real-world setting.

METHODS: Prestudy use checks involved 2 actuations of the MDI, with a further 2 performed 2 hours later. Within-study monitor checks, performed before dispensing at clinic visits 2 to 4, included a computerized check of monitor clock function, actuation accuracy, and battery life. Within-study data checks involved computerized checks of monitor clock function before data upload.

RESULTS: Two thousand six hundred seventy-eight of 2728 monitors (98.2%) passed prestudy use checks. Seventy-six of

2642 monitors (2.9%) dispensed to participants failed within-study monitor checks. Fifty-one of 2642 monitors (1.9%) malfunctioned before data upload, mostly as a result of fluid immersion. Ninety-three of 2642 monitors (3.5%) were lost or thrown away by participants. Complete data was available from 2498 of 2642 dispensed monitors (94.5%) and 2498 of 2549 returned monitors (98.0%).

CONCLUSIONS: The Smartinhaler Tracker is a reliable monitor for measuring MDI use in a real-world setting. Use of extensive monitor and data-checking protocols reduces data loss. In a research or clinical setting, the use of a validated and reliable electronic monitor represents the reference standard for assessing patterns of medication use. © 2012 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1:83-91)

Key words: Adherence; Asthma; Electronic; Metered-dose inhaler; Monitoring; Patterns of use; Smartinhaler; Validation

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Abbreviations used

MDI- Metered-dose inhaler

RCT- Randomized controlled trial

SMART- Single combination inhaler as Maintenance And Reliever Therapy

STANDARD- Fixed-dose combination inhaler as maintenance therapy with short-acting beta agonist as reliever

Use of inhaled asthma treatments in clinical trials is traditionally measured by patient self-report or daily diary¹⁻⁴ or by the use of electronic monitors that record inhaler actuation.⁵⁻⁸ Self-report and daily diaries have been shown to be unreliable methods to quantify medication usage,^{9,10} probably because of a combination of recall bias and patients documenting what they perceive their clinician wishes to see. Electronic monitors have the advantage of being objective¹¹ and can provide data on patterns of medication use.¹² Several electronic monitors have been developed over the past 20 years, for both metered-dose inhaler (MDI) and dry powder inhaler use.^{13,14} The reliability and utility of these monitors has been variable.^{15,16} Investigator-led “quality control” processes before and during patient use are advocated, in addition to detailed reporting of the performance and reliability of these monitors.¹⁷

Recently, the Smartinhaler Tracker (Nexus6 Limited, Auckland, New Zealand) has been developed as an electronic monitor of MDI use.¹⁸ It comprises a plastic casing (the monitor), into which a conventional medication canister can be inserted. The monitor casing incorporates a battery, switch, and electronics that record the number, date, and time (to the nearest second) of the depression of the canister during actuation. Thus, the monitor combined with a medication canister can be used to measure use of inhaled therapy delivered via an MDI. The Smartinhaler Tracker has been used to measure adherence to therapy and patterns of medication use in clinical studies in both adults^{12,19,20} and children.²¹⁻²⁴

This monitor has been validated for use in short-term laboratory (“bench”) studies.^{25,26} These studies reported an accuracy between 98% and 100% in recording actuations, provided that medication canisters were inserted firmly into the monitors. We have also completed a 6-month *in vitro* validation of the monitor, with the testing undertaken in standardized laboratory conditions.²⁷ Two of 22 monitors failed checks of monitor function before use in this study. The validation process highlighted the importance of performing preuse checks to identify malfunctioning devices before dispensing. The monitor was 99.7% accurate in recording the number of actuations and 99.3% accurate in recording the date and time of actuations. Data storage on the monitor over an 8-week period, data upload, and battery charge were found to be highly reliable. However, because these studies were all undertaken in a bench setting, they have limited generalizability when applied to a clinical or trial setting.

We have recently undertaken a randomized controlled trial (RCT) of combination inhaled corticosteroid/long-acting beta agonist therapy (budesonide/formoterol MDI; Vannair; AstraZeneca Limited, Auckland, New Zealand) when taken as part of a single maintenance and reliever therapy regime (SMART therapy) or as a fixed-dose treatment with short-acting beta agonist as reliever (STANDARD therapy). Participants’ use of

medication was measured with the Smartinhaler Tracker MDI electronic monitor. The aim of this analysis is to report on the performance of these monitors in a real-world setting, based on extensive pretrial and within-trial validation protocols for their use.

METHODS**RCT design**

The study was a 24-week multicenter, prospective, open-label RCT of SMART versus STANDARD therapy in patients with asthma aged 16 to 65 years (Australian New Zealand Clinical Trials Registry no. ACTRN12610000515099). Eligible patients had a physician’s diagnosis of asthma and a current prescription for inhaled corticosteroid, with at least 1 asthma exacerbation in the preceding year. Key exclusion criteria included a diagnosis of chronic obstructive pulmonary disease or an onset of respiratory symptoms after the age of 40 in current or ex-smokers with a ≥ 10 pack-year smoking history. The study was undertaken at 5 centers in New Zealand (4 primary care centers and 1 secondary care center).

Participants were randomly assigned at a 1:1 ratio to receive 200/6 μg budesonide/formoterol via MDI, 2 actuations twice daily as maintenance with extra doses for relief of symptoms as per the SMART regime²⁸ (SMART group), or 200/6 μg budesonide/formoterol via MDI 2 actuations twice daily as maintenance with salbutamol via MDI (100 μg per actuation; Ventolin; GlaxoSmithKline NZ Limited, Auckland, New Zealand) for relief of symptoms²⁹ (STANDARD group). Five study visits occurred over 24 weeks, at weeks 0 (randomization visit), 3, 10, 17, and 24.

All participants provided written informed consent, and the New Zealand Multi-Region Ethics Committee approved the study protocol.

Smartinhaler Tracker MDI electronic monitor

The Smartinhaler Tracker electronic monitors were designed to allow a Vannair medication canister or a Ventolin medication canister to be inserted for actuation (Figure 1, A and B). Each actuation of the MDI resulted in a date and time log, which was stored on the monitor for the study window. The data were then uploaded after the next study visit, via the Internet, to a website-based database, using a USB (Universal Serial Bus) computer connection and dedicated software (Connection Centre; Nexus6 Limited).

Inhalers used by patients before enrollment were collected from them at visit 1. For the STANDARD group, 1 budesonide/formoterol and 1 salbutamol MDI were provided for the initial 3-week study window. Two budesonide/formoterol and 2 salbutamol MDIs were provided for the 7-week study windows. One further budesonide/formoterol and salbutamol MDI each were also provided in sealed envelopes at visits 1 to 4, as emergency backup inhalers. For the SMART group, 2 budesonide/formoterol MDIs were provided for the initial 3-week study window. Three budesonide/formoterol MDIs were provided for the 7-week study windows. One further budesonide/formoterol MDI was provided in a sealed envelope at visits 1 to 4, as the emergency backup inhaler. Participants were able to use their study inhalers concurrently during the study window if they wished. All participants were asked to keep their MDIs free from moisture during trial participation and were reminded to not discard used or empty inhalers. Participants were informed that

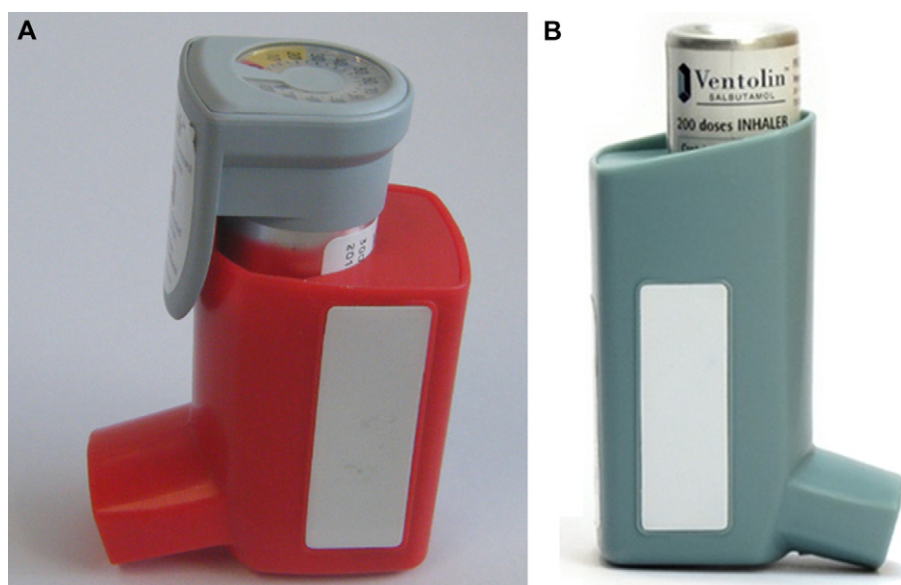


FIGURE 1. Smartinhaler Tracker for budesonide/formoterol (Vannair MDI) (A) and for salbutamol (Ventolin MDI) (B).

their inhalers contained an electronic device that measured the total number of actuations used and were unaware of the detailed capabilities of the monitor to record patterns of use.

At study visits 2 to 5, all the previously dispensed MDIs were collected from participants and were set aside for upload after the study visit. Replacement MDIs, including emergency MDIs,

were issued to participants for the next study period. After the study visit was completed, data upload was performed from all the collected MDIs. The plastic monitor casings were reused, so that after data upload, new medication canisters were inserted into the monitors, in preparation for dispensing at the next visit. Monitors remained patient specific during the trial. Each

TABLE I. Prestudy and within-study monitor and data-checking protocol

Monitor checks	Prestudy monitor check*	Within-study monitor check†	Within-study data check‡
Loading with medication canister‡	X	X	
Reset§	X	X	X
Check for external structural faults	X	X	
Prestudy MDI actuations¶	X		
Within-study MDI actuations¶		X	
Diary log of actuations	X		
Computerized testing process		X	
Check of accuracy of number of actuations	X	X	
Check of accuracy of actuation time and date	X	X	
Check of monitor ID number**	X	X	
Check of battery charge	X	X	
Printable test report generated		X	
Preview of data stored on monitor††	X		X
Computerized check of monitor clock accuracy‡‡			X
Data from faulty monitors prevented from upload to website			X
Upload of data from functioning monitors to website			X
Data retrieval and cleanup from faulty monitors			X
Fault analysis for malfunctioning monitors	X	X	X

ID, Identification.

*Prestudy checks were performed at the coordinating trial site before study use.

†Within-study monitor checks and data checks were performed by investigators during trial use.

‡The MDI was actuated during every canister reload to ensure firm insertion of the canister.

§Data were cleared from the monitor memory, and the clock was synchronized with the computer.

¶The MDI was actuated twice, with a further 2 actuations at least 2 hours later.

¶The MDI was actuated twice, prompted by computer software TEST function.

**Each monitor had a unique identification number visible externally and on computer connection.

††Visual inspection of data on the monitor without upload to the website.

‡‡Computerized check of monitor clock accuracy to ± 15 minutes of actual time.

TABLE II. Characteristics of trial participants

	SMART group*	STANDARD group†
Age (y), mean $\pm$ SD	41.3 $\pm$ 13.7	42.6 $\pm$ 14.5
Male/female, no. (%)	48 (31.8)/103 (68.2)	46 (30.3)/106 (69.7)
Duration of asthma diagnosis (y), mean $\pm$ SD	26.7 $\pm$ 14.5	26.2 $\pm$ 14.6
FEV ₁ (L), mean $\pm$ SD	2.62 $\pm$ 0.91	2.50 $\pm$ 0.78
FEV ₁ percent predicted, mean $\pm$ SD	81.6 $\pm$ 18.9	80.4 $\pm$ 20.5
ACQ-7 Score, mean $\pm$ SD	1.87 $\pm$ 0.96	1.90 $\pm$ 1.13

FEV₁, Forced expiratory volume in 1 second; ACQ-7, Asthma Control Questionnaire-7.

*Treatment was 200/6 μ g budesonide/formoterol MDI (Vannair) 2 actuations twice daily as maintenance therapy with extra doses for relief of symptoms as per the SMART regime (n = 151 participants).

†Treatment was 200/6 μ g budesonide/formoterol MDI (Vannair) 2 actuations twice daily as maintenance therapy with salbutamol (Ventolin) 100 μ g for relief of symptoms (n = 152 participants).

STANDARD patient therefore had a minimum allocation of 5 budesonide/formoterol monitors and 5 salbutamol monitors for the 24-week trial period. Each SMART patient had a minimum allocation of 7 budesonide/formoterol monitors for the 24-week trial period. A separate stock of replacement monitors was also available to each trial site to substitute for lost, damaged, or malfunctioning monitors.

Monitor and data-checking protocols

The 3 components of monitor and data checking (prestudy monitor checks, within-study monitor checks, and within-study data checks) are summarized in Table I.

Prestudy monitor-checking protocol

All monitors were loaded with study medication canisters and tested at the coordinating trial site with the use of the following protocol before patient use (prestudy use checks). The MDI was first reset by connecting to a computer via a USB connection with the use of the dedicated software (this cleared the monitor memory and synchronized the monitor clock to the computer clock). Two actuations were performed and recorded on a paper diary. A further 2 actuations were then performed at least 2 hours later. The number, date, and time of the 4 actuations, as well as the unique monitor identification number, were then checked for accuracy by comparing the data stored on the monitor with the paper diary. MDIs that were 100% accurate were reset and ready for use. Any MDIs that failed this prestudy check were removed from circulation and returned to the manufacturer for further fault analysis. Testing was undertaken by 1 of 2 trained investigators under standardized conditions.

Within-study monitor-checking protocol

Monitors loaded with medication canisters were checked for correct functioning by investigators before dispensing to patients at visits 2, 3, and 4. The purpose of the within-study monitor checks was to ensure that there had been no loss of function in the period after prestudy checks and to identify damaged monitors before repeat dispensing. The within-study testing process was computerized to minimize the time taken to perform the checks while maximizing accuracy. The protocol was as follows: an MDI was connected to the computer and the TEST function was selected. The monitor was automatically reset by the software. Investigators were prompted by the computer

software to actuate the MDI twice. The software compared the monitor clock with the computer clock and checked the monitor battery as well as the number and time/date of the 2 actuations performed. The monitor was considered to have failed testing if the battery was not fully charged (ie, less than 5 of 5 bars). At the end of the TEST function, the monitor was automatically reset, and the monitor clock was synchronized with the computer. If all elements of monitor check were accurate, the software displayed a green tick to inform the investigator that the MDI could be used in the trial. If any elements of the check failed, investigators were prompted with a red cross and were advised to remove the monitor from circulation and to return to the coordinating site. Test reports were saved or printed for reference. Investigators were advised to perform the checks in the 48 hours before the study visit.

Within-study participant data-checking protocol

Data from the MDIs collected from participants at visits 2, 3, 4, and 5 were uploaded after the study visit. Investigators first connected the MDI to the computer via a USB cable and previewed the data. This allowed investigators to view stored data on the MDI. Data were then uploaded to a password-protected website database. The computer software automatically compared the monitor clock with the computer clock before data upload; a time discrepancy of 15 minutes or more prevented data upload and prompted the investigator to return the MDI to the coordinating site for analysis. This function allowed monitors with incorrect clocks to be identified before data transfer, thus reducing the risk of erroneous data being uploaded to the database. Malfunctioning monitors were subsequently sent from the coordinating trial site to the manufacturer for fault analysis. A 15-minute discrepancy was allowed because the product information for the Smartinhaler specifies that the monitor clock accuracy is ± 15 minutes per year without update.

After successful data upload, the monitor was automatically reset so that the memory was clear of data logs. The monitor was then reloaded with a new medication canister, in preparation for use at the next visit.

RESULTS

Three hundred three participants (151 SMART and 152 STANDARD) were randomly assigned to treatment. The baseline characteristics of the participants are summarized in Table II. Actuations (n = 282,466) from participant use of their inhalers over 49,149 days of treatment exposure were stored on the database at study completion.

Prestudy monitor checks

A total of 2728 monitors (839 salbutamol monitors and 1889 budesonide/formoterol monitors) underwent prestudy checks. Of the 2728 monitors tested, 2678 (98.2%) passed this check (Figure 2). Of the 50 monitors that failed testing, 26 did not record actuations that were performed, 20 recorded extra actuations, and 4 had structural faults. Of these 50 monitors, 15 were subsequently repaired and passed for use in the trial, whereas the remaining 35 monitors were not used any further.

Within-study monitor checks

We dispensed 2642 monitors (806 salbutamol monitors and 1836 budesonide/formoterol monitors) to patients in the trial. A total of 93 of 2642 monitors (3.5%; 33 budesonide/formoterol

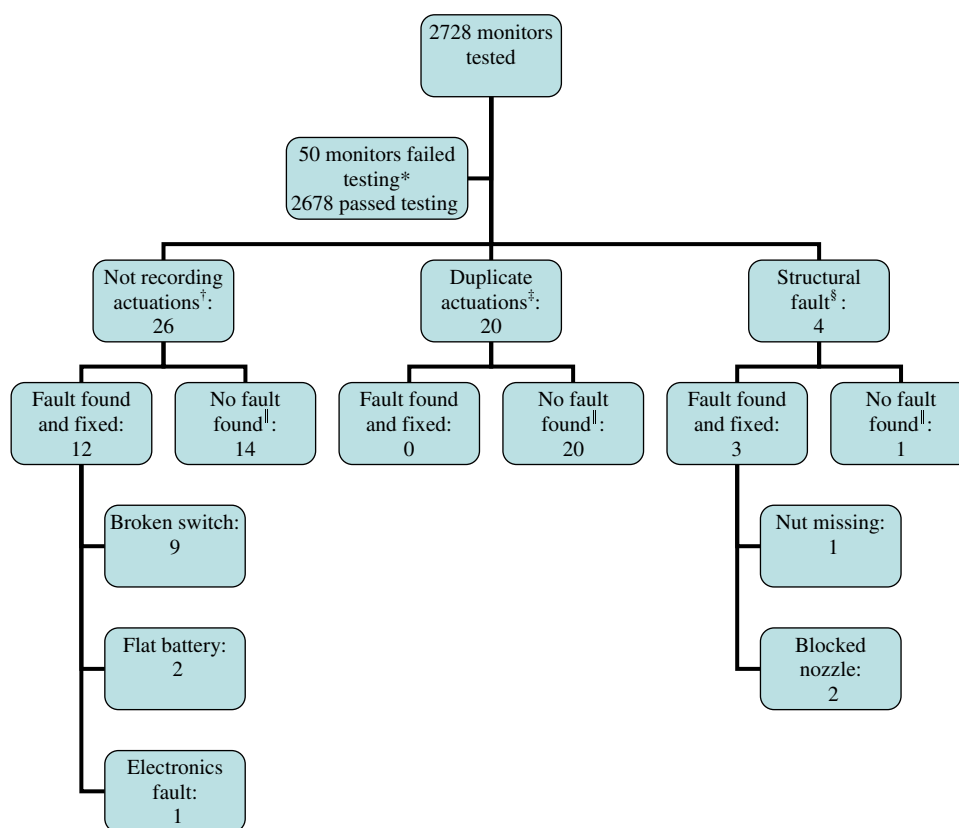


FIGURE 2. Monitors identified as faulty during prestudy use checks. *Twenty-seven budesonide/formoterol monitors and 23 salbutamol monitors; †10 budesonide/formoterol monitors and 16 salbutamol monitors; ‡16 budesonide/formoterol monitors and 4 salbutamol monitors; §1 budesonide/formoterol monitor and 3 salbutamol monitors; ¶these devices were not reused in the trial.

monitors in the SMART group and 29 budesonide/formoterol and 31 salbutamol monitors in the STANDARD group) were lost or thrown away by participants during the study.

Seventy-six monitors (2.9% of the total dispensed) failed testing and were removed from trial use by investigators as a result of the within-study monitor-checking process (Figure 3). Thirty-three of those monitors failed testing because the battery was not fully charged; in 31 of those monitors, actuation recording was not affected. Twenty-five monitors failed checks because of a medication plume fault as a result of MDI nozzle blockage, and 12 did not record test actuations correctly. Four monitors were found to record duplicate actuations.

Within-study participant data checks

Fifty-one monitors (1.9% of the total dispensed) failed the data upload checks (Figure 4). In all cases, data were stored on the monitor from use of the MDI during the preceding study window. An error message from the computer software alerted the investigator that there was a fault, preventing data transfer, or that the monitor clock had malfunctioned. In most of the monitors, evidence of fluid immersion as the cause for malfunction was determined during manufacturer analysis. All of these monitors were returned to the manufacturer, and in 48, data could be retrieved to the point of monitor malfunction. In 3 monitors, data extraction was unable to be performed because of the severity of fluid damage.

Overall monitor performance

Ninety-three of 2642 monitors (3.5%) were lost or thrown away by participants. Fifty-one of 2642 monitors (1.9%) malfunctioned before data upload. Complete data was therefore available from 2498 of 2642 dispensed monitors (94.5%) and from 2498 of 2549 returned monitors (98.0%).

DISCUSSION

To our knowledge, this is the first study to provide detailed information on the performance of an electronic monitor in a real-world setting. This study has shown that the Smartinhaler Tracker is a highly reliable monitor of MDI use by patients and that implementing an extensive pretrial and within-trial monitor- and data-checking process can help to safeguard data acquisition. In pretrial checks, 98% of monitors were found to be fully functional and ready for patient use. The pretrial checks identified a minority of malfunctioning devices that required repair before dispensing, highlighting the importance of investigator-led postproduction testing of monitor function. The within-trial checking process allowed monitors damaged by patient use to be identified and removed from circulation, thus reducing the occurrence of data loss as a result of device malfunction. The rate of complete data loss because of missing monitors was 3.5% (93 of 2642 monitors), whereas data loss because of monitor malfunction in returned devices was 1.9% (51 of 2642 monitors). With the use of systems incorporated into the software used

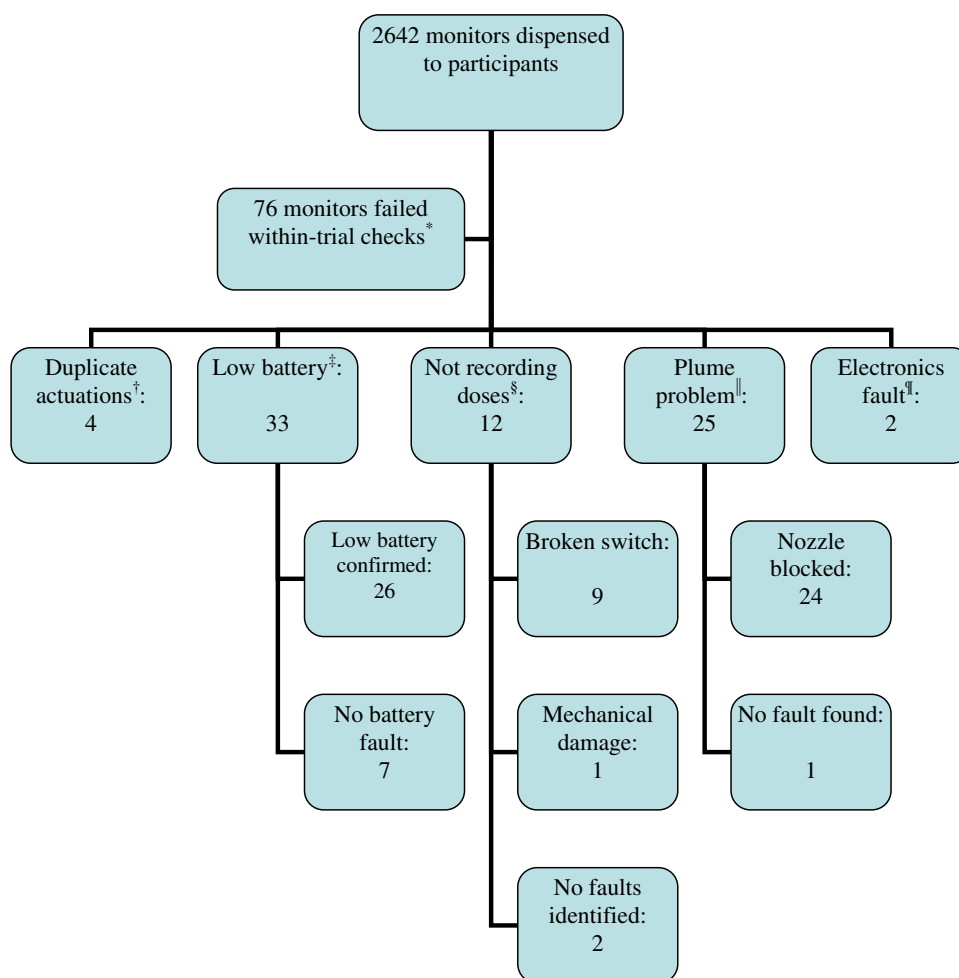


FIGURE 3. Monitors identified as faulty during within-study checks at visits 2 to 4. *Thirty-seven budesonide/formoterol monitors and 39 salbutamol monitors; †3 budesonide/formoterol monitors and 1 salbutamol monitor (no fault found on these monitors; not reused in the trial); ‡23 budesonide/formoterol monitors and 10 salbutamol monitors; §7 budesonide/formoterol monitors and 5 salbutamol monitors; ||4 budesonide/formoterol monitors and 21 salbutamol monitors; ¶2 salbutamol monitors.

for monitor upload, data that were potentially corrupted were identified and prevented from database entry. The performance of the monitor- and data-checking systems justifies the use of this technology as the optimal method to measure inhaled MDI medication use.

A major strength of this study was its real-world design. The recruitment strategy and inclusion/exclusion criteria allowed patients with comorbidities and patients who were most at risk of poor adherence to be enrolled. As a result of this strategy, monitors are likely to have been exposed to similar environmental conditions as conditions found in real-life use of inhalers by patients. We suggest that this greatly improves the generalizability of our findings, regarding the performance of the monitors.

Monitor fault before trial use was largely a consequence of specific device-related issues, such as broken switches and hardware faults. Although the occurrence of these faults was limited to less than 2% of the monitors tested, the use of the prestudy checks allowed these monitors to be identified before patient use and reduced the occurrence of data loss. This finding is in

agreement with prior recommendations that electronic monitors should undergo investigator-led testing before patient use and that the use of a prestudy quality-control process can help to reduce the occurrence of data loss.³⁰

Complete data was available from 2498 of 2642 monitors (94.5%) dispensed to patients in this trial. Of the 144 monitors from which there was missing data, approximately two-thirds (93/144) were lost or thrown away by patients in this real-world study, despite repeated advice to the contrary. Thus, complete data in 2498 of 2549 returned monitors (98.0%) were present. In the remaining 51 of returned monitors (2.0%), monitor malfunction prevented complete data retrieval. In comparison, a trial in 380 patients with asthma reported a 14.7% monitor failure rate with the MDILog and an additional 1.6% of missing monitors.⁷ In another recent study that measured adherence in 333 patients using the Diskus Adherence Logger and MDILog, 20% of monitors failed to download.⁵ A prior pediatric study reported that 8% of Doser CT monitors failed with mechanical faults.³¹ Smartinhaler malfunction during trial use was generally a consequence of a combination of patient- and monitor-related

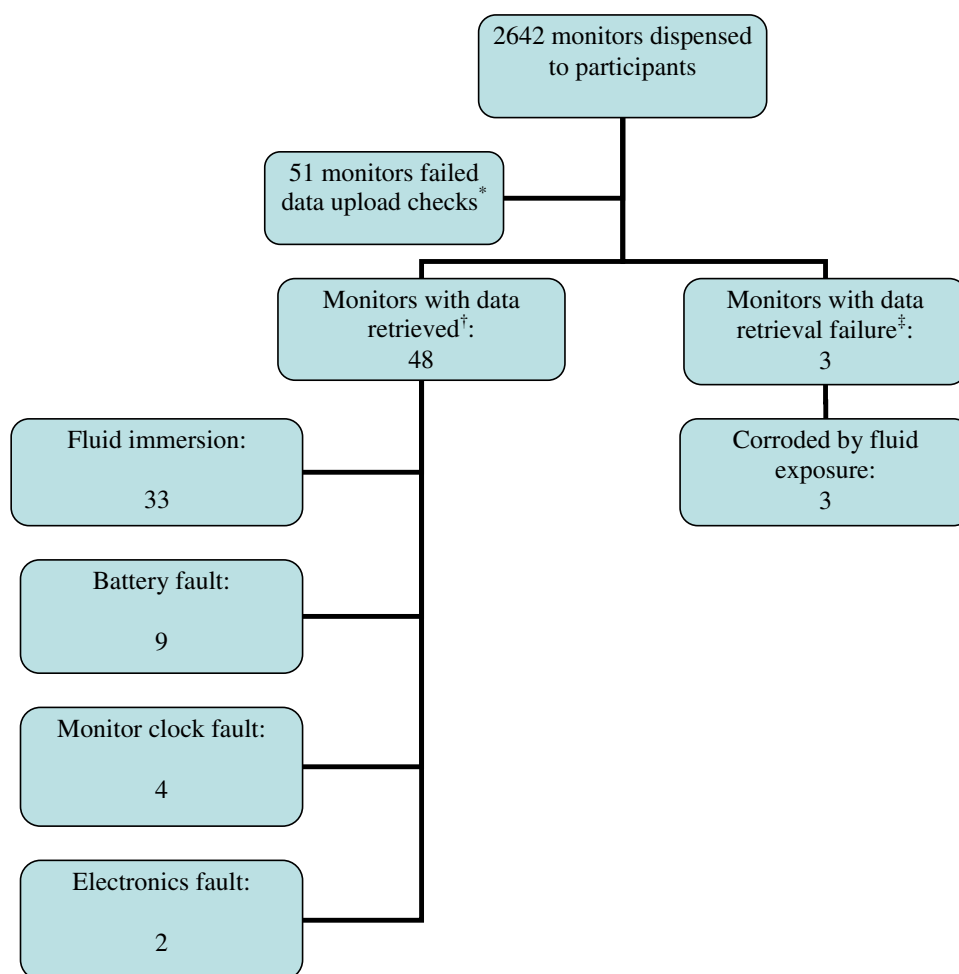


FIGURE 4. Monitors identified as faulty during within-study data upload checks at visits 2 to 5. *Thirty-two budesonide/formoterol monitors and 19 salbutamol monitors; †29 budesonide/formoterol monitors and 19 salbutamol monitors; ‡3 budesonide/formoterol monitors.

factors. Problems such as fluid immersion, low battery, or electromechanical damage are likely to have been caused by both real-world use of MDIs by patients and the inherent vulnerability of electronic monitors to damage from environmental conditions. Many of these risks are difficult to reduce without affecting patient behavior, which could then affect the generalizability of the data obtained. However, the within-trial checks allowed identification and subsequent removal of malfunctioning devices from further use and were a key factor in limiting data loss.

Our study has also highlighted the importance of real-time data-checking processes to identify erroneous data before inclusion in the central database and to reduce the occurrence of data loss. In the 51 monitors with stored medication use data that were identified as malfunctioning before data upload in our study, data could be retrieved and cleaned, up to the point of malfunction, in 48 monitors. This process was performed continuously throughout the study and therefore reduced the time to database lock at trial completion.

We observed that in 35 of 2728 monitors (1.3%) that failed checks before use, specific reasons for these failures could not be determined in the subsequent manufacturer analysis. Monitor faults that occurred intermittently may be one explanation for

this finding. These monitors were not dispensed to participants. Although intermittent faults in recording actuations in dispensed monitors might also occur, our bench study found greater than 99% monitor accuracy over 24 weeks of testing (2176 actuations performed, with 6 unrecorded and 4 extra actuations recorded).²⁷ A specific issue highlighted by the within-trial checks was the occurrence of problems with the plume of medication on actuation with 24 monitors. The majority of these were salbutamol monitors (21 of 24 monitors). One possible explanation for this is that Ventolin formulated with hydrofluoroalkane propellants may build up around the MDI actuator and cause blockage, if the MDI is not washed regularly.³² The consumer medicine information for Ventolin in New Zealand advises patients to wash their inhaler every week.³³ However, given that patients were instructed to keep their inhalers dry because of the electronic components of their monitors, washing of inhalers was not possible. Both this factor and the re-use of monitors between study visits may have influenced the occurrence of plume problems seen in our study.

In our study, we have reported on the performance and testing of 2 MDI monitors from a single manufacturer. Monitoring of treatment delivered with other inhaler devices, for example, dry

powder inhaler, or using MDI monitors of alternative design, is also important. We suggest that the design and conduct of our trial-checking protocols, as well as the sources of monitor malfunction, are equally applicable to other monitors that use similar technology. Two further components of testing, which can help to establish monitor validity, include canister weighing as a validation of the total number of doses administered in a clinical trial and bench testing in a laboratory setting. We have previously found that a detailed bench testing process is important in establishing long-term monitor validity and for informing subsequent clinical trial quality control protocols.²⁷

The lessons learned about methods to limit data loss and the need for close cooperation with monitor manufacturers both before and during clinical trial conduct are relevant to researchers and developers of technology in the field of inhaled medication adherence monitoring. We would advocate detailed reporting of the quality control processes and performance of monitors during clinical trial use. These procedures may not necessarily require all of the components that we have used in our study, and protocols that are designed to be relevant to the study and the monitor are suggested. This will allow more informed interpretation of results and will provide important information to researchers considering the use of electronic monitors in future trials.

In summary, this is the first trial to report on the real-world performance of an electronic monitor to measure inhaled asthma treatment, and it builds on the experience gained from prior studies that used electronic adherence monitoring.^{5,34} The Smartinhaler Tracker is a highly reliable monitor of MDI use in a real-world setting. Pre-use and within-trial checks allowed identification and removal of malfunctioning monitors and reinforced the importance of comprehensive trial protocols to maximize data integrity when using electronic monitors.^{30,35} Given the importance of adherence measurement in both clinical³⁶⁻³⁸ and clinical trial settings,^{39,40} we suggest that electronic monitoring of inhaled therapy, using validated monitors and with careful quality control processes, is the reference standard when information on patterns of use of medication is required.

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