BMJ Open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-009350
Article Type:	Protocol
Date Submitted by the Author:	09-Jul-2015
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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Communication, Medical education and training, Nursing, Patient-centred medicine
Keywords:	Adult thoracic medicine < THORACIC MEDICINE, Asthma < THORACIC MEDICINE, MEDICAL EDUCATION & TRAINING

A protocol for a randomised clinical trial of the effect of providing feedback on inhaler technique and adherence from an electronic device in poorly controlled severe asthma patients.

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Keywords
Severe asthma; adherence; INCA electronic monitor; Randomized controlled trial; inhaler technique.

Word Count: 3,430

Abstract

Introduction

In clinical practice it is difficult to distinguish between patients with refractory asthma from those with poorly controlled asthma, where symptoms persist due to poor adherence, inadequate inhaler technique or co-morbid diseases. We designed an audio recording device which, when attached to an inhaler, objectively identifies the time and technique of inhaler use, thereby assessing both aspects of adherence. This study will test the hypothesis that feedback on these two aspects of adherence to patients improves adherence and helps clinicians distinguish refractory from difficult to control asthma.

Methods

This is a, single blind, prospective randomized clinical trial performed at 5 research centers. Patients with partially controlled or uncontrolled severe asthma who have also had at least one severe asthma exacerbation in the prior year are eligible to participate. The effect of two types of nurse delivered education interventions to promote adherence and inhaler technique will be assessed. The active group will receive feedback on their inhaler technique and adherence from the new device over a three month period. The control group will also receive training in inhaler technique and strategies to promote adherence but no feedback from the device. The primary outcome is the difference in actual adherence, a measure that incorporates time and technique of inhaler use between groups at the end of the third month. Secondary outcomes include the number of patients who remain refractory despite good adherence, and differences in the components of adherence after the intervention. Data will be analyzed on an intention-to-treat and a per protocol basis. The sample size is 220 subjects (110 in each group) and loss to follow-up is estimated at 10% which will allow result to show a 10% difference (0.8 power) between group means with a Type I error probability of 0.05.

Registration: Clinicaltrials.gov NCT01529697

INTRODUCTION

Approximately 10% of patients with asthma remain poorly controlled with persisting symptoms and severe exacerbations despite use of combination therapy with long acting beta agonists and inhaled corticosteroids. This poor control may be due to medication refractory asthma or due to difficult to manage asthma from issues such as poor inhaler technique, poor adherence or co-existing comorbid disease[1-3]. In practice distinguishing refractory from difficult to manage asthma is difficult. For example, adherence to medications, a particular problem in patients with severe asthma, is difficult to detect since self-report is unreliable [4]and pharmacy refill records only identify if the individual has collected a prescription. Some patients may demonstrate a reasonable inhaler technique when directly observed, but may be careless in their inhaler use on a day-to-day basis [5]. Hence, without objective longitudinal information on inhaler adherence and technique it is challenging to distinguish a patient with refractory asthma from one who has difficult to manage asthma.

We developed a device, INhaler Compliance Assessment device (INCA™), which makes a digital audio recording of an inhaler being used [5-12]. Analysis of the audio recordings, by automated signal processing techniques, provides an objective assessment of both the time of inhaler use and the technique of inhaler use. We hypothesized that this information could be used both as part of an educational consultation for patients and for clinicians to help distinguish refractory from difficult to manage asthma.

We describe the protocol of a randomised single blind, nurse delivered education study. The study will comprise of patients with severe asthma attending specialist hospital asthma clinics, who remain uncontrolled and have experienced at least one recent severe asthma exacerbation. Based on information obtained from the INCA™ acoustic

recording device, one group will discuss patterns of adherence and training on technique of inhaler use. The second group will be given strategies to improve adherence while technique errors will be corrected using checklists [13]. Adherence will be assessed objectively in all subjects using the INCA™ electronic recording device. Global outcomes will be quantified using the clinical, lung function adherence and exacerbation data collected during the observation period.

METHODS

Sponsorship

This is a researcher initiated study, funded by the Health Research Board of Ireland (HRB)(Pro/2011/57) and hosted within the Dublin Centre for Clinical Research (DCCR) clinical trials centres. The study sponsor, RCSI, is an independent Medical University. The trial was approved by the Beaumont Hospital's Ethics committees. The trial is registered as NCT01529697 on Clinicaltrials.gov and a detailed statistical plan has been approved by an independent statistical team. The INCA™ device was manufactured and supplied by Vitalograph, Ennis, Ireland and GlaxoSmithKleine provided the salmeterol/fluticasone diskus inhaler for this study.

Setting

This is a prospective, multi-centre, single blind randomized controlled trial of two nurse delivered strategies to optimise inhaler technique and adherence of patients with Stage 3 to 5 asthma. The study is being conducted at the Clinical Research Centres of five University Hospitals. At each centre between one and three nurses have been trained to provide either intervention. The study period is from 2011 with ongoing recruitment.

Participants

Asthma diagnosis is made using a clinician diagnosis supported by one or more of the -following: obstructive spirometry with 10% reversibility, either spontaneously over time or with inhaled beta agonist or with 15% peak flow variability over time or through a positive bronchial provocation challenge.

Inclusion criteria

Patients already prescribed therapy equivalent to step 3 or higher on the Asthma Management Guidelines for at least 3 months and who had at least one exacerbation treated with systemic glucocorticoids in the prior year and who are either uncontrolled or partially controlled by GINA guidelines are eligible for inclusion [1].

Exclusion criteria

Patients who are controlled, as defined by the GINA criteria [1] on their current therapy. Additional exclusion criteria are those who are unwilling to participate in a clinical study or prior hypersensitivity to salmeterol/ fluticasone. There are no other exclusion criteria.

Study design

The study flow is indicated in Table 1.

Study Procedure	Visit 1	Visit 2	Visit 3	Visit 4
Informed Consent	X			
Demographics	X			
Medical History	X			
Inclusion & exclusion Criteria	X			
Current medications	X			
Physical Examination	X			X
Vital signs	X	X	X	X
AQLQ	X	X	X	X
Randomisation	X			
Dispense adapted Seretide inhaler	X	X	X	
Dispense adapted Ventolin inhaler as required	X	X	X	
Dispense electronic PEFR monitor	X	X	X	
Download device readings active only		X	X	X
Inhaler use education	X	X	X	X
Adverse events		X	X	X
Concomitant medications		X	X	X

Table 1: Details of Study data collection The Active group receive a copy of devise readings and active feedback about adherence and inhaler technique, Visit 1: Screening Visit: at time of enrolment (Week 0); Visit 2: at end of month one (Week 4); Visit 3: at end of month two (Week 8); Visit 4: Final Visit at the end of month three (Week 12).

Patients identified at specialist asthma clinics who meet the inclusion and not the exclusion criteria are invited to participate in the study. Once consented each study visit is performed by a registered nurse.

The dose of inhaled corticosteroid and LABA is not changed.

The audio recording technology has not yet been established for the turbohaler, hence, for those participants who are currently prescribed formoterol/budesonide their therapy is changed to an equivalent dose of salmeterol/fluticasone delivered via a diskus device.

At the initial visit the participant's age, sex, height, weight, duration of asthma, smoking history, number of courses of steroids in the prior year are recorded. The dose of salmeterol/fluticasone and duration of taking this dose, use and dose of other inhaled therapy including short acting beta agonists, LAMA, nasal steroid and antihistamines are recorded. The nurse records the PEFR and an Inhaler Proficiency checklist Score (IPS; Appendix 1), a ten point checklist score. The Asthma Control Test (ACT) score and Asthma Quality of Life Questionnaire (AQLQ) are completed by the participant. Serum

total and specific immunoglobulin E levels and peripheral blood eosinophil levels, prior spirometry and bronchial provocation test are recorded from the clinical notes.

The participants receive a salmeterol/fluticasone diskus inhaler with an INCA™ device attached and they are asked to use the inhaler twice per day and to take reliever salbutamol, as required, for break through symptoms. Participants are asked to record their peak expiratory flow with an electronic monitor (ASMA-1, Vitalograph, Ennis, Ireland) twice daily.

Visits are scheduled 4, 8 and 12 weeks later. At these, the participants return their inhaler and electronic Peak flow monitor. Additionally, at each of these visits the ACT, AQLQ, PEFR as well as any exacerbations and changes in medications, including new medications are recorded. Due to an omission in the original protocol the ACT has not been recorded on the first 60 participants. The training, as per allocation, is then given. Details of the clinical visits are included in the clinical training manual, Appendix 2.

Interventions

Control group: Behavioural intervention and inhaler training

The key points of each of the visit consultations includes; participant identified goals for outcomes, exploration of barriers to achieving goals, explanation of the purpose of asthma treatment and provision of an asthma management plan for exacerbations. A checklist is used to review and correct errors in inhaler technique (IPS). To promote adherence during the education emphasis is given on the individual developing a habit in time of use of the inhaler. Four, 8 and 12 weeks later the participants return their inhaler and receives an identical structured consultation as at the first meeting. A video and manual describing the exact steps of usual care is shown as https://www.youtube.com/watch?v=PlTkhVuogaI

Active group: Feedback using recordings from the INCA Device

The content of the first visit was the same as for the control group. At the second, third and fourth visits the participants together with the nurse review the information recorded on the INCA device and electronic PEFR, in the form of a graph. This graph includes a structured consultation that focuses on the time of use, patterns of inhaler use attempting to identify barriers to good adherence, development of habit of use as well as remediation of errors of inhaler use, as identified by the analysis the data.

Data collection

The INCA Device

The original INCA™ device was designed at the Department of Bioengineering, TCD, Ireland and CE marked and manufactured by Vitalograph, Ennis, Ireland.

Analysis of the audio data

Analysis of the digital recordings are performed as previously described [5]. The files are uploaded to a server and analysed using signal processing methods. The sensitivity and specificity details have been published [6]. Two independent raters over-read all files from all patients. Their agreed, combined analysis will be used in the calculation of the actual adherence. These raters are unaware of either the patient allocation or any of the patient clinical outcomes and are not involved in any aspect of the patient care during the trial. Critical inhaler errors including whether the drug was primed, whether the patient exhaled after priming but before inhalation, whether an adequate flow rate was achieved, the exact flow rate, whether there were multiple inhalations indicating inadequate breath-holds and correct sequence of events/timing of events were performed. Non-critical errors such as not holding the device level were not recorded.

The sensitivity and agreement between raters and between raters and the algorithm have been published [8] .

Objectives

The objective of this study is to assess if feedback obtained from the INCA™ device on adherence and technique errors yields better adherence and better clinical information than best practice.

Primary outcome

The actual inhaler adherence, expressed as cumulative drug exposure, is calculated by combining the time of use along with the interval between doses and incorporating, by audio analysis, if the inhaler was used correctly. The rate of actual adherence at the end of the intervention will be compared between the active and control patients.

Secondary outcome analysis will include:

A global clinical outcome profile, see Table 2 comprising the observed adherence, peak flow data, asthma control, quality of life and reliever use as well as, exacerbations over the study period will be calculated. The numbers in each of the groups who proceed in the next 6 months to further therapy, in particular omalizumab, after they finish the study will be compared.

	Non-adherence	Refractory Asthma	Controlled Asthma	Co-morbidity
Actual adherence > 80%	No	Yes	Yes of No	Yes
PEFR >80 of AUC	Yes or No	No	Yes	Yes
AQLQ >5 and ACT >19	Yes or No	No	Yes	No
Exacerbations	Yes or No	Yes or No	No	Yes or No

Table 2: Clinical Decision tool. The outcome decision tool, at the end of the study the cumulative information on actual adherence, PEFR rate, calculated as the AUC within 80% of normal predicted, ACT and AQLQ considered to be optimal and exacerbations will be used to describe one of four possible outcomes; sufficiently non-adherent as the likely reason for failure to progress, asthma that is refractory because despite optimal adherence both symptoms and lung function and exacerbations occur, controlled asthma, patients in whom there are no longer impaired nor have exacerbations, and a group of patients who have good adherence and lung function but who continue to have symptoms therefore suggesting that a significant co-morbidity is likely driver for the ongoing symptoms.

Comparison of the proportion of patients in each group who achieved full adherence at the end of the study (≥80%), as well as changes in patterns of adherence in the two groups, the number progressing to good actual technique will be assessed. A comparison of the morning and evening habit of inhaler use, error rates, overdose rates, interval and attempted rates of adherence in the two groups at the end of the study will be compared. The factors associated with improving adherence will be described.

The relationship between adherence and asthma control, asthma quality of life and PEFR will be assessed by comparing the proportion of patients who are GINA 2011, ACT controlled and are no longer requiring regular beta agonist. The ACT, PEFR rate, AQLQ and reliever use between the two groups will also be compared.

The Kappa score between raters and a sensitivity analysis of the algorithm will be calculated.

Sample size calculation

The usual rate of adherence to inhalers is reported to be calculated from dose counter and is expressed as an average adherence. Most studies in trials of patients with inhalers report adherence of >0.8. Therefore, we anticipate that there is going to be high adherence in the setting of a clinical trial. However, we also expect that there will be a number of patients with poor inhaler technique which will lead to a lower actual adherence. We shall assume that when this is accounted for then the actual adherence is 0.15 lower, ie: 0.65 adherence at the end of the first month. Our preliminary data in primary care and on the wards indicates a standard deviation of adherence is 0.25 [5]. The primary endpoint is the rate of adherence at the end of the study period, ie: during the last visit at month three between active and control groups. We expect the adherence to improve over the study period in the control group, as they are repeatedly educated in inhaler use by 0.05 and we expect the active group to get closer to the physician reported ideal rate of 0.8, i.e. a 0.15 improvement in actual adherence. Hence, with a power of 0.8 at the 0.05 significance level, with a 0.1 difference in the actual adherence rate then a sample size of 100 in each limb is required. We expect a 10% dropout; hence the target recruitment sample size is 210 in total.

Randomisation and allocation.

Randomisation will use a stratified by site random block design, with blocks varying in size of 8-12. Allocation Ratio is 1:1 with a central computer generated randomisation. This is a single blind study, the nurse may deliver either intervention and is not blinded to the allocation. The participants are aware which group they are allocated to and aware that data on adherence is being collected for analysis.

Statistical Methods

Data analysis

Data will be analyzed on an intention-to-treat and a per protocol basis. Data will be presented as means with standard deviations and Student's t test will be used to compare differences in proportions between the groups. Significance will be set at the 5% level. Stratification of patients by new versus old with respect to use of the Diskus device, stratification based on severity of disease according to GINA guidelines.

Discussion

Most management guidelines suggest that for poorly controlled asthma patients that before changing therapy, issues with adherence and inhaler technique need to be addressed [1-3]. However, this is difficult to achieve in clinical practice. The aim of this study is to see if a nurse delivered educational intervention with repeated education and monitored adherence can improve both aspects of adherence, the time and the technique of inhaler use. We will record when and how well an individual has used their inhaler over time with a device that makes a digital audio recording of an individual using their inhaler. Analysis of the recorded time of use, the interval between use and technique of use provides a measure termed actual adherence. The study's primary outcome will be a comparison of the actual adherence between the two groups, at the end of the third month of participation in the study.

It is expected that over the study period some patients will become fully controlled. while others will remain poorly controlled despite being fully adherent over the study period and others may remain uncontrolled but also poorly adherent. This information may help with clinical decision making for individual patients for example by helping decide whom should have their therapy increased, their inhaler device changed or further interventions to promote adherence such as motivational interviewing Hence, by combining clinical outcomes with the longitudinally collected adherence, asthma control and PEFR data, the composite outcome may assist a clinician in identifying the cause of difficult to manage asthma and increase the clinical confidence that the patient has refractory asthma.

This study has several novel features; this is the first to use a technology that objectively assesses adherence to inhalers both in terms of technique of use as well as time of use. This technology involves not simply the device but also the automated algorithms, the feedback tools and the content of the feedback delivered by the nurse during the consultation.

It could be argued that the results of this clinical research study, performed in a research setting, will lead to greatly improved adherence, which is not reflective of clinical practice. The authors see no alternative way of performing the study as practical challenges in a more real world setting may lead to a significant loss of patient follow up and hence less precise information. Another limitation of the study is that it has a limited follow up time frame, hence the long-term effect on clinical outcomes and persistence of the observed benefits will not be established.

In summary, this study proposes to assess the impact of a series of consecutive education visits on adherence and inhaler use by patients with severe asthma. In addition by combining objective measurement of lung function, clinical outcomes and objectively assessed adherence this may also provide clinicians greater precision in decision making for the future care of this group of patients.

Abbreviations

ACT; asthma control test, AQLQ; asthma quality of life score, INCA; inhaler compliance aid, PEFR; peak expiratory flow rate. IPS; inhaler proficiency score.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RR, CH and RC conceived the INCA device. RC conceived and designed the study. EMacH, IS, GD, SD and MF each made substantial contributions to study design; JS, MH, TT, IS, SD, IK, WR have all been involved in defining the characteristics of the INCA device and the associated acoustic and other analysis. GC provided the statistical support and contributed to the drafting of the manuscript. All authors were involved in the writing of the manuscript and revising it critically for intellectual content; and have given final approval of the version to be published. All authors read and approved the final manuscript.

Acknowledgements

This study is funded by the Health Research Board of Ireland. The authors would like to thank Deidre Hyland, John McCourt and D Kenny RCSI Centre for Clinical Research; Professors D Kelleher, and P Murray from the Dublin Centre for Clinical Research; Eavan Daly and Cheryl Marron from GSK; Frank Keane and Enda Kelly from Vitalograph Ireland; the research staff of the Centres for Clinical Research at St Vincent's Hospital, Adelaide, Meath and National Children's Hospital (AMNCH), St James's Hospital and Cork University Hospital.

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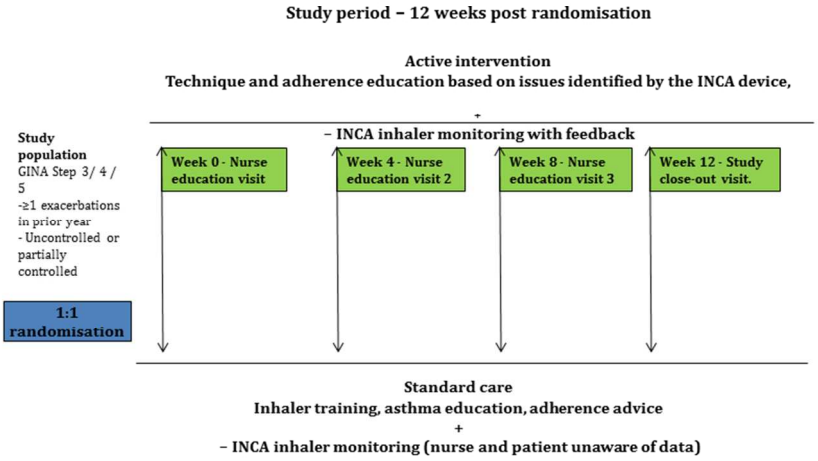
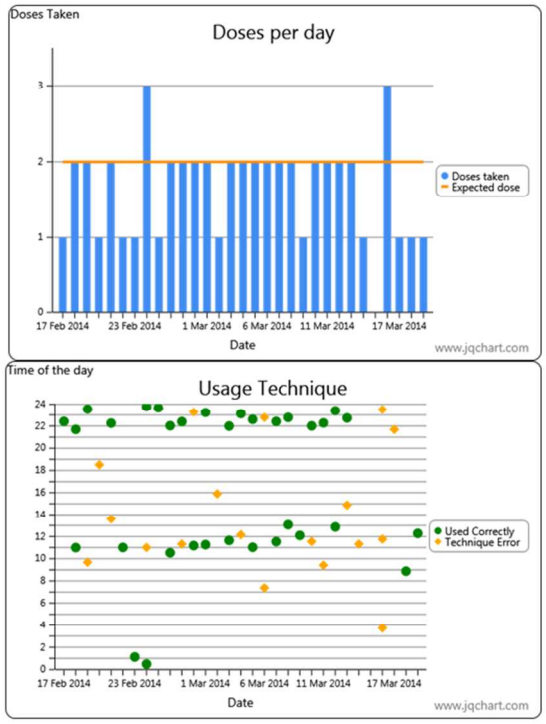


The study participants are patients with a diagnosis of asthma attending a severe asthma clinic who remain uncontrolled or partially controlled and have experienced at least one severe exacerbation of asthma in the prior year. With no medication change adherence and inhaler technique are re-enforced over the 12 week monitoring period.
254x190mm (96 x 96 DPI)



A screen shot of the data presented to the patient for discussion of their adherence to the salmeterol/fluticasone diskus inhaler over the prior month. In this example the patient has good time of use, in particular in the evening, suggesting they are developing a regular habit of use. However, they show intermittent errors in inhaler technique, in this example they used the inhaler incorrectly on almost half of all occasions in which the inhaler was used.
254x190mm (96 x 96 DPI)

Appendix 1

Inhaler Proficiency Schedule (IPS)

Patient ID: _____

Date: _____

Visit No: _____

	YES	NO
Does the patient hold the outer casing of the inhaler in one hand, whilst pushing the thumb grip away, until a click is heard?		
Does the patient hold the inhaler with mouthpiece towards himself?		
Does the patient slide lever away until it clicks?		
Does the patient hold the inhaler in a horizontal position?		
Does the patient breath out slowly and then put inhaler in front of mouth?		
Does the patient place mouthpiece between lips and breathe in as deeply as possible?		
Does the patient remove inhaler from mouth and hold breath for about 10 seconds?		
After 10 seconds does the patient breathe out slowly?		
Does the patient close the inhaler by sliding thumb grip back towards himself as far as it will go until it clicks?		
Does the patient gargle throat after use?		

Appendix 2

Clinical Training Manual

Including examples

Please note – throughout the manual, established behaviour change techniques are noted in parentheses, in accordance with the Behaviour Change Taxonomy (Michie et al., The Behavior Change Technique Taxonomy (v1) of 93 Hierarchically Clustered Techniques: Building an International Consensus for the Reporting of Behavior Change Interventions. Ann Behav Med 2013, 46: 81-95)

Summary

The "Best practice care" group

The principal themes of "Best practice care" group are:

1. Asthma education (nature of disease and need for treatment) and discussion on adherence, including-strategies to enhance adherence e.g. reminders and goal setting.

2. Training on inhaler use till proficient, as demonstrated with an Inhaler Proficiency Score (IPS, see appendix 2) observational score.

3. Advice on allergen or trigger avoidance; as related to PEFR.

The INCA group

The core features are listed:

1. The patient's treatment goal is established and used as the focus of the conversation. [This goal is to be referred to at each visit]

2. Data from the INCA device including (1) time of use, (2) pattern of using, to maximise habit forming (3) handling proficiency including inhalation flow rates are discussed, with graphs as shown in figure 2. These are aimed to enhance the value of the inhaler.

3. Data from the hand held PEFR, reliever use and AQLQ are correlated with the adherence so that these can be used to account for improvements or declines in these measures, to identify triggers

Screening visit/ Randomisation visit

Active and Control

"Tell me about your asthma and its treatment"

Opens the goals for treatment discussion, the rationale for treatment, and the inhaler technique.

All will have asthma explained as follows:

"Asthma is a clinical disease where the airways are irritated and swollen by dust, viruses, pollens and pollution. This irritation causes narrowing of the air passages which leads to you feeling tight, wheezy and short of breath" [5.1, 9.1]

All will have asthma treatment explained:

"Asthma is treated with an inhaler which has medicines which open the airways, to reduce the feelings of tightness and shortness of breath as well as a medicine which relieves the irritation, a steroid. The treatment that seems to work best is an inhaler that has two medicines, one to open the airways and the other lessens the inflammation and together they are very effective at treating most people's asthma. We think that using this type of medicine regularly helps keep you well"

"Any questions?"

"Are you happy with this explanation?"

Then:

"What would you say your goals for getting better are? List up to three, as specific as possible" [1.3].

Then:

At Visit 1 all participants (Active and Control) will demonstrate their INHALER TECHNIQUE and will be educated accordingly using the teach-to-goal approach. The IPS score after training will be recorded, **aiming** to reach 9/10. [6.1; 4.1].

Then:

All are shown how to use the PEFR meter [6.1.; 4.1].

At this visit, the physiological, clinical, past history and health status questionnaires are collected, see CRF.

Visits 2 to 4; every 4 weeks (21-30 days) for 12 weeks.

Control Group

Reviews progress over the last month

"How did you get on and how are you?"

"Have you been to the Doctor for your chest in the last month?"

Review of ACT, AQLQ peak flow measurements [2.2.;2.7.]

"How have you been getting on with your inhaler?"

This is an opportunity to promote strategies to encourage inhaler adherence e.g. try and identify some regular routine that the participant frequently does and tie in taking their inhaler at that time. For example "What time do you have dinner?" "Go to bed?" "Watch the news?" Link these to inhaler use. [7.1.;8.1.;8.3.]

INCA ACTIVE Group

"How did you get on and how are you?"

"Have you been to the Doctor for your chest in the last month?

Review of primary goals [1.7, possibly 1.6]. The old and the current ACT score is the focus of the discussion.

"What was it about your **asthma**/**health**/**goals** that you want to make better?"

"To achieve these aims need you to use your inhaler as best you can. It's really only after a few months of this that we can really see a big impact, eg changing/reducing your medication use."

"To get these goals, let us see if we can help you get the most from your inhaler."

Step 1 Doses/ timings graph (Figure 2). Focus on the positive aspects [2.7, 10.4]. For example "Well done you remember to take your inhaler most days ", or, "you are steady in the morning times, showing you have a good routine but the evening needs a little work". Try to identify some regular routine that the participant frequently does and tie in taking their inhaler at that time. For example "What time do you have dinner?" "Go to bed?" "Watch the news?" [7.1,8.1,8.3]. This is an opportunity to discuss barriers [1.2, possibly 12.1,

12.2] to regular inhaler use with the patient and for them to make suggestions on how they can link inhaler use with their asthma progress [5.1.;2.2].

Step 2. From the graphs, the errors are identified including exhalation, low peak inspiratory flow rates (peak inspiratory flow rate achieved on using the inhaler. If there was an error in handling the salmeterol/fluticasone inhaler this can be corrected using the teach-to-goal technique [4.1.]. If there are examples of low inspiratory flow then these are pointed out and further training, eg with the Clement Clark device is given. [2.2, 2.6]

Step 3 is the PEFR readings.–The day to day peak to trough variation and The weekly trend as well as (going up, staying the same, getting better) can then be related to the inhaler use, (going up, staying the same, getting better). [2.6.]

These data provide a point for the patient to discuss the outcomes in relation to their own life, e.g. if they were away, were in stressful situations, if they developed a URI, etc. [1.5]

Step 4. Inhaler reliever inhaler use. This is collected on the second INCA device, which is attached to a salbutamol inhaler. Note, the use of a reliever has been shown to be a good surrogate of adherence.

Step 5 combination graph where all the information on adherence, PEFR and symptoms are collated. These graphs provide a point for the patient to discuss reliever use in relation to their own life, eg if they were breathless, were in stressful situations [4.2], if they developed a URI, and if these coincide with PEFR changes or prior poor adherence [1.5] or if falling rates of inhaler use reflect increasing adherence to preventer therapy. This can be used as a reminder and a tool for discussing possible causes of exacerbations or loss of asthma control [1.5, 1.7].

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Page 1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Page 2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Page 3-4
	2b	Specific objectives or hypotheses	Page 11
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Pages 7-11
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Page 5-6
Participants	4a	Eligibility criteria for participants	Page 5-6
	4b	Settings and locations where the data were collected	Page 5-6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Page 9-10
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Page 11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Page 13
Sample size	7a	How sample size was determined	Page 13
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Page 14
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Page 14
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Page 14
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Page 14
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	NA

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Page 14
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Page 14
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	NA
Recruitment	14a	Dates defining the periods of recruitment and follow-up	NA
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	NA
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	NA
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	NA
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	NA
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	NA
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	NA
Other information			
Registration	23	Registration number and name of trial registry	Page 2
Protocol	24	Where the full trial protocol can be accessed, if available	Appendix 2
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Page 17

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

A protocol for a randomised clinical trial of the effect of providing feedback on inhaler technique and adherence from an electronic device in poorly controlled severe asthma patients.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009350.R1
Article Type:	Protocol
Date Submitted by the Author:	04-Sep-2015
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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Communication, Medical education and training, Nursing, Patient-centred medicine
Keywords:	Adult thoracic medicine < THORACIC MEDICINE, Asthma < THORACIC MEDICINE, MEDICAL EDUCATION & TRAINING

A protocol for a randomised clinical trial of the effect of providing feedback on inhaler technique and adherence from an electronic device in poorly controlled severe asthma patients.

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Keywords
Severe asthma; adherence; INCA electronic monitor; Randomized controlled trial; inhaler technique.

Word Count: 3,430

Abstract

Introduction

In clinical practice it is difficult to distinguish between patients with refractory asthma from those with poorly controlled asthma, where symptoms persist due to poor adherence, inadequate inhaler technique or co-morbid diseases. We designed an audio recording device which, when attached to an inhaler, objectively identifies the time and technique of inhaler use, thereby assessing both aspects of adherence. This study will test the hypothesis that feedback on these two aspects of adherence to patients improves adherence and helps clinicians distinguish refractory from difficult to control asthma.

Methods

This is a, single blind, prospective randomized clinical trial performed at 5 research centers. Patients with partially controlled or uncontrolled severe asthma who have also had at least one severe asthma exacerbation in the prior year are eligible to participate. The effect of two types of nurse delivered education interventions to promote adherence and inhaler technique will be assessed. The active group will receive feedback on their inhaler technique and adherence from the new device over a three month period. The control group will also receive training in inhaler technique and strategies to promote adherence but no feedback from the device. The primary outcome is the difference in actual adherence, a measure that incorporates time and technique of inhaler use between groups at the end of the third month. Secondary outcomes include the number of patients who remain refractory despite good adherence, and differences in the components of adherence after the intervention. Data will be analyzed on an intention-to-treat and a per protocol basis. The sample size is 220 subjects (110 in each group) and loss to follow-up is estimated at 10% which will allow result to show a 10% difference (0.8 power) in adherence between group means with a Type I error probability of 0.05.

Registration: Clinicaltrials.gov NCT01529697

INTRODUCTION

Approximately 10% of patients with asthma remain poorly controlled with persisting symptoms and severe exacerbations despite use of combination therapy with long acting beta agonists and inhaled corticosteroids [1]. This poor control may be due to medication refractory asthma or due to difficult to manage asthma from issues such as poor inhaler technique, poor adherence or co-existing comorbid disease[1-3]. In practice distinguishing refractory from difficult to manage asthma is difficult. For example, adherence to medications, a particular problem in patients with severe asthma, is difficult to detect since self-report is unreliable [4]and pharmacy refill records only identify if the individual has collected a prescription. Some patients may demonstrate a reasonable inhaler technique when directly observed, but may be careless in their inhaler use on a day-to-day basis [5]. Hence, without objective longitudinal information on inhaler adherence and technique it is challenging to distinguish a patient with refractory asthma from one who has difficult to manage asthma [6]

We developed a device, INhaler Compliance Assessment device (INCA™), which makes a digital audio recording of an inhaler being used [5, 7-13]. Analysis of the audio recordings, by automated signal processing techniques, provides an objective assessment of both the time of inhaler use and the technique of inhaler use. Validation of the device and the audio recordings have been previously presented [5, 7-13]. We hypothesized that this information could be used both as part of an educational consultation for patients and for clinicians to help distinguish refractory from difficult to manage asthma.

The objective of this study is to assess if inhaler use obtained from the INCA™ device on time of use and technique of use leads to better inhaler adherence and better clinical information than best practice.

METHODS

We describe the protocol of a randomised single blind, nurse delivered education study. The study will comprise of patients with severe asthma attending specialist hospital asthma clinics, who remain uncontrolled and have experienced at least one recent severe asthma exacerbation. Based on information obtained directly from the INCA™ acoustic recording device, one group (the active arm) will discuss patterns of adherence and training on technique of inhaler use. The second group (the control arm) will be given generalised strategies to improve adherence while technique errors will be corrected using checklists [14]. Adherence will be assessed objectively in all subjects.. Global outcomes will be quantified using the clinical, lung function adherence and exacerbation data collected during the observation period.

Sponsorship

This is a researcher initiated study, funded by the Health Research Board of Ireland (HRB)(Pro/2011/57) and hosted within the Dublin Centre for Clinical Research (DCCR) clinical trials centres. The study sponsor, Royal College of Surgens (RCSI), is an independent Medical University. The trial was approved by the Beaumont Hospital's Ethics committees. The trial is registered as NCT01529697 on Clinicaltrials.gov and a detailed statistical plan has been approved by an independent statistical team. The INCA™ device was manufactured and supplied by Vitalograph, Ennis, Ireland and GlaxoSmithKline provided the salmeterol/fluticasone diskus inhaler for this study.

Setting

This is a prospective, multi-centre, single blind randomized controlled trial of two nurse delivered strategies to optimise inhaler technique and adherence of patients with Stage 3 to 5 asthma. The study is being conducted at the Clinical Research Centres of five University Hospitals within the republic of Ireland (4 in Dublin County, 1 in Cork

County). At each centre between one and three nurses have been trained to provide either intervention. The lead clinical nurse was educated by the priniciapl investigator and a respiratory nurse specialist. All other nurses were educated by our lead clinical nurse in a teach to goal method with demonstration. The study period is from 2011 with ongoing recruitment.

Participants (n=210)

Prior to study recruitment an asthma diagnosis is made using a clinician diagnosis supported by one or more of the -following: obstructive spirometry with a minimum of10% reversibility, either spontaneously over time or with inhaled beta agonist or with a minimum 15% peak flow variability over time or through a positive bronchial provocation challenge.

Inclusion criteria

Patients already prescribed therapy equivalent to step 3 or higher on the Asthma Management Guidelines (1) for at least 3 months and who had at least one exacerbation treated with systemic glucocorticoids in the prior year and who are either uncontrolled or partially controlled by GINA guidelines are eligible for inclusion [1]. Patients must also be 18 years or older in age.

Exclusion criteria

Patients who are controlled, as defined by the GINA criteria [1] on their current therapy. Additional exclusion criteria are those who are unwilling to participate in a clinical study, current smokers or prior hypersensitivity to salmeterol/ fluticasone. There are no other exclusion criteria.

Study design

The study flow is indicated in Table 1.

Study Procedure	Visit 1	Visit 2	Visit 3	Visit 4
Informed Consent	X			
Demographics	X			
Medical History	X			
Inclusion & exclusion Criteria	X			
Current medications	X			
Physical Examination	X			X
Vital signs	X	X	X	X
AQLQ	X	X	X	X
ACT	X	X	X	X
Randomisation	X			
Dispense adapted Seretide inhaler	X	X	X	
Dispense electronic PEFR monitor	X	X	X	
Download device readings active only		X	X	X
Inhaler use education	X	X	X	X
Adverse events Recorded		X	X	X
Concomitant medications Recorded		X	X	X

Table 1: Details of Study data collection The Active group receive a copy of device readings and active feedback about adherence and inhaler technique, Visit 1:

Screening Visit: at time of enrolment (Week 0); Visit 2: at end of month one (Week 4); Visit 3: at end of month two (Week 8); Visit 4: Final Visit at the end of month three (Week 12). AQLQ = Asthma Quality of Life Questionaire, ACT= Asthma Control Test, PEFR= Peak Expiratory Flow Rate

Patients identified at specialist asthma clinics who meet the inclusion and not the exclusion criteria are invited to participate in the study. Once consented each study visit is performed by a registered nurse.

The dose of inhaled corticosteroid and Long Acting Beta-Agonist (LABA) is not changed at recruitment and during the study procedure, as the main aim of the study is to improve adherence to current asthma treatment.

The audio recording technology has not yet been established for the turbohaler or the pMDI, hence, for those participants who are currently prescribed formoterol/budesonide/beclamethasone, at recruitment, their therapy is changed to an equivalent dose of salmeterol/fluticasone delivered via a diskus device. This change is made by the physician looking after the patient in the outpatient clinic. Following this the patient is then referred to the study. The patient may still refuse to enter the study. All other aspects of regular patient care are continued.

At the initial visit the participant's age, sex, height, weight, duration of asthma, smoking history, number of courses of steroids in the prior year are recorded (self-reported by the participant). The dose of salmeterol/fluticasone and duration of taking this dose, use and dose of other inhaled therapy including short acting beta agonists, Long Acting Muscarinic Antagonist (LAMA), nasal steroid and antihistamines are recorded. The

nurse records the Peak Expiratory Flor Rate (PEFR) and an Inhaler Proficiency checklist Score (IPS; Appendix 1), a ten point checklist score. The Asthma Control Test (ACT) score and Asthma Quality of Life Questionnaire (AQLQ) (15)are completed by the participant. Serum total and specific immunoglobulin E levels and peripheral blood eosinophil levels, prior spirometry and bronchial provocation test are recorded from the clinical notes.

The participants receive a salmeterol/fluticasone diskus inhaler with an INCA™ device attached and they are asked to use the inhaler twice per day and to take reliever salbutamol, as required, for break through symptoms. All participants are informed at recruitment that the device would provide information on how and when they use their inhaler. Participants are asked to record their peak expiratory flow with an electronic monitor (ASMA-1, Vitalograph, Ennis, Ireland) twice daily.

Visits are scheduled 4, 8 and 12 weeks later, summarised in Figure 1. At these, the participants return their inhaler and electronic Peak flow monitor. Additionally, at each of these visits the ACT, AQLQ, PEFR as well as any exacerbations and changes in medications, including new medications are recorded. Due to an omission in the original study protocol, where ACT was not a measured variable, ACT has not been recorded on the first 60 participants. The training, as per allocation, is then given. Details of the clinical visits are included in the clinical training manual, Appendix 2.

Interventions

Control group: Behavioural intervention and inhaler training

The key points of each of the visit consultations includes; participant identified goals for outcomes, exploration of barriers to achieving goals, explanation of the purpose of asthma treatment and provision of an asthma management plan for exacerbations. A

checklist is used to review and correct errors in inhaler technique (IPS). To promote adherence during the education emphasis is given on the individual developing a habit in time of use of the inhaler. Four, 8 and 12 weeks later the participants return their inhaler and receives an identical structured consultation as at the first meeting. Participants and nursing staff are unaware of data from the INCA device in the control arm. A video and manual describing the exact steps of usual care is shown as https://www.youtube.com/watch?v=PlTkhVuogaI

Active group: Feedback using recordings from the INCA Device

The content of the first visit was the same as for the control group. At the four, eight and twelve weeks later the participants together with the nurse review the information recorded on the INCA device and electronic PEFR, in the form of a graph, see Figure 2 for an example of graphs produced by the INCA device. This graph leads to a consultation that focuses on the time of use, patterns of inhaler use attempting to identify barriers to good adherence, development of habit of use as well as remediation of errors of inhaler use, as identified by the analysis the data.

Data collection

The INCA Device

The original INCA™ device was designed at the Department of Bioengineering, TCD, Ireland and CE marked and manufactured by Vitalograph, Ennis, Ireland.

Analysis of the audio data

Analysis of the digital recordings are performed as previously described [5]. The files are uploaded to a server and analysed using signal processing methods. For patients in the active arm, these audio recordings are uploaded during the visit by the nurse and

feedback is given to the patient based on an automated analysis of the audio files. The sensitivity and specificity details have been published [7].

At a later date two independent raters over-read all files from all patients. Their agreed, combined analysis will be used in the calculation of the actual adherence. These raters are unaware of either the patient allocation or any of the patient clinical outcomes and are not involved in any aspect of the patient care during the trial. Critical inhaler errors including whether the drug was primed, whether the patient exhaled after priming but before inhalation, whether an adequate flow rate was achieved, the exact flow rate, whether there were multiple inhalations indicating inadequate breath-holds and correct sequence of events/timing of events were performed. Non-critical errors such as not holding the device vertically (as described by the manufacturer) were not recorded. The sensitivity and agreement within the two raters and between the raters and the algorithm have been published [9] . Any disagreements within raters was reviewed by a third rater who made the final decision on the audio file.

Electronic Peak Expiratory Flow Rate (ePEFR)

Participants receive an ePEFR device at each visit, which are then collected at the subsequent visit. For participants in the active arm, data from these devices are downloaded during the visit and information on PEFR, in conjunction with adherence data from the INCA device, are feedback to the participant.

Objectives

The objective of this study is to assess if feedback obtained from the INCA™ device on adherence and technique errors yields better adherence and better clinical information than best practice.

Primary outcome

The actual inhaler adherence, expressed as cumulative drug exposure, is calculated by combining the time of use along with the interval between doses (correct time is twice a day, in a period not less than 6 hours between the last dose and the subsequent dose or at a time greater than 18 hours apart from the previous dose.) and incorporating, by audio analysis, if the inhaler was used correctly (ie. no evidence of critical technique errors mentioned above). The rate of actual adherence for the last month of the intervention will be compared between the active and control patients.

Secondary outcome analysis will include:

Clinical outcomes, PEFR, ACT, AQLQ, reliever use and exacerbations between active and control arms at the end of the study will be compared. A composite score of these values, the global clinical outcome profile, see Table 2 comprising the observed adherence, peak flow data, asthma control, quality of life and reliever use as well as, exacerbations over the study period will be calculated. Exacerbations is defined as an increase in symptoms (ie shortness of breath, wheeze, cough) requiring a course of systemic glucocorticoids. Healthcare utilisation (ie. unscheduled GP visits, hospitalization and emergency department visits) will also be compared between active and control arms.

	Non-adherence	Refractory Asthma	Controlled Asthma	Co-morbidity
Actual adherence > 80%	No	Yes	Yes or No	Yes
PEFR >80 of Area Under the Curve (AUC)	Yes or No	No	Yes	Yes
AQLQ >5 and ACT >19	Yes or No	No	Yes	No

Exacerbations	Yes or No	Yes or No	No	Yes or No

Table 2: Clinical Decision tool. The outcome decision tool, at the end of the study the cumulative information on actual adherence, PEFR rate, calculated as the AUC within 80% of normal predicted, ACT and AQLQ considered to be optimal and exacerbations will be used to describe one of four possible outcomes; sufficiently non-adherent as the likely reason for failure to progress, asthma that is refractory because despite optimal adherence both symptoms and lung function and exacerbations occur, controlled asthma, patients in whom there are no longer impaired nor have exacerbations, and a group of patients who have good adherence and lung function but who continue to have symptoms therefore suggesting that a significant co-morbidity is likely driver for the ongoing symptoms.

Comparison of the proportion of patients in each group who achieved full adherence at the end of the study (≥80%), as well as changes in patterns of adherence in the two groups, the number progressing to good actual technique will be assessed. A comparison of the morning and evening habit of inhaler use, error rates, overdose rates, interval and attempted rates of adherence in the two groups at the end of the study will be compared. The factors associated with improving adherence will be described.

The relationship between adherence and asthma control, asthma quality of life and PEFR will be assessed by comparing the proportion of patients who are GINA 2011, ACT controlled and are no longer requiring regular beta agonist. The ACT, PEFR rate, AQLQ and reliever use between the two groups will also be compared.

The Kappa score between raters and a sensitivity analysis of the algorithm will be calculated.

Sample size calculation

The usual rate of adherence to inhalers is reported to be calculated from dose counter and is expressed as an average adherence. Most studies in trials of patients with inhalers report adherence of >0.8. Therefore, we anticipate that there is going to be high adherence in the setting of a clinical trial. However, we also expect that there will be a number of patients with poor inhaler technique which will lead to a lower actual adherence. We shall assume that when this is accounted for then the actual adherence is 0.15 lower, ie: 0.65 adherence at the end of the first month. Our preliminary data in primary care and on the wards indicates a standard deviation of adherence is 0.25 [5]. The primary endpoint is the rate of adherence at the end of the study period, ie: during the last visit at month three between active and control groups. We expect the adherence to improve over the study period in the control group, as they are repeatedly educated in inhaler use by 0.05 and we expect the active group to get closer to the physician reported ideal rate of 0.8, i.e. a 0.15 improvement in actual adherence. Hence, with a power of 0.8 at the 0.05 significance level, with a 0.1 difference in the actual adherence rate then a sample size of 100 in each limb is required. We expect a 10% dropout; hence the target recruitment sample size is 210 in total.

Randomisation and allocation.

Randomisation will use a stratified by site random block design, with blocks varying in size of 8-12. Allocation Ratio is 1:1 with a central computer generated randomisation. This is a single blind study, the nurse may deliver either intervention and is not blinded to the allocation. The participants are aware which group they are

allocated to and aware that data on adherence is being collected for analysis. Patients in the control arm will be blinded to their adherence data from the INCA™ device.

Statistical Methods

Data analysis

Data will be analyzed on an intention-to-treat and a per protocol basis. Data will be presented as means with standard deviations and Student's t test will be used to compare differences in mean adherence rates between the groups. Significance will be set at the 5% level. Stratification of patients by new versus previous use with respect to use of the Diskus device (ie. if patient's are using the Diskus device for the first time, or if they have previously used the device), stratification based on severity of disease according to GINA guidelines.

Discussion

Most management guidelines suggest that for poorly controlled asthma patients that before changing therapy, issues with adherence and inhaler technique need to be addressed [1-3]. However, this is difficult to achieve in clinical practice. The aim of this study is to see if a nurse delivered educational intervention with repeated education and monitored adherence can improve both aspects of adherence, the time and the technique of inhaler use. We will record when and how well an individual has used their inhaler over time with a device that makes a digital audio recording of an individual using their inhaler. Analysis of the recorded time of use, the interval between use and technique of use provides a measure termed actual adherence. The study's primary outcome will be a comparison of the actual adherence between the two groups, at the end of the third month of participation in the study.

It is expected that over the study period some patients will become fully controlled. while others will remain poorly controlled despite being fully adherent over the study period and others may remain uncontrolled but also poorly adherent. This information may help with clinical decision making for individual patients for example by helping decide whom should have their therapy increased, their inhaler device changed or further interventions to promote adherence such as motivational interviewing Hence, by combining clinical outcomes with the longitudinally collected adherence, asthma control and PEFR data, the composite outcome may assist a clinician in identifying the cause of difficult to manage asthma and increase the clinical confidence that the patient has refractory asthma.

This study has several novel features; this is the first to use a technology that objectively assesses adherence to inhalers both in terms of technique of use as well as time of use. This technology involves not simply the device but also the automated algorithms, the feedback tools and the content of the feedback delivered by the nurse during the consultation.

It could be argued that the results of this clinical research study, performed in a research setting, will lead to greatly improved adherence, which is not reflective of clinical practice. Additionally both control and active patients will be reviewed on a monthly basis for three months. This approach itself will more than likely also lead to an increase in adherence in the active and control group and may not fully reflect 'usual care.' To add to this patients in both the active and control arm are aware that their inhaler use is being 'monitored' and this may lead to increased inhaler adherence. The authors see no alternative way of performing the study as practical challenges in a more real world setting may lead to a significant loss of patient follow up and hence less precise information. The benefits of regular visits and PEFR measurements outweigh the disadvantages. Another limitation of the study is that it has a limited follow up time frame, hence the long-term effect on clinical outcomes and persistence of the observed benefits will not be established.

In regards to safety, patients enrolled in this study have to be uncontrolled or partially controlled by GINA guidelines. However, for the duration of the study their regular medical treatment of their asthma will not be changed (ie. their ICS/LABA dose will remain unchanged). The rationale behind this, is to see the effect three months of adherence training would have on asthma control, potentially reducing the need to increase patient medication (step-up) and possibly allowing physicians to reduce

asthma treatment (step-down). Patients can withdraw at any time during the study without any impact on their clinical care. Additionally if the clinician feels there is a clinical indication, patients can be removed from the study for the patient's best interest.

In summary, this study proposes to assess the impact of a series of consecutive education visits on adherence and inhaler use by patients with severe asthma. In addition by combining objective measurement of lung function, clinical outcomes and objectively assessed adherence this may also provide clinicians greater precision in decision making for the future care of this group of patients.

Abbreviations

ACT; asthma control test, AQLQ; asthma quality of life score, INCA; inhaler compliance aid, PEFR; peak expiratory flow rate. IPS; inhaler proficiency score.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RR, CH and RC conceived the INCA device. RC conceived and designed the study. EMacH, IS, GD, SD and MF each made substantial contributions to study design; JS, MH, TT, IS, SD, IK, WR have all been involved in defining the characteristics of the INCA device and the associated acoustic and other analysis. GC provided the statistical support and contributed to the drafting of the manuscript. All authors were

involved in the writing of the manuscript and revising it critically for intellectual content; and have given final approval of the version to be published. All authors read and approved the final manuscript.

Acknowledgements

This study is funded by the Health Research Board of Ireland. The authors would like to thank Deidre Hyland, John McCourt and D Kenny RCSI Centre for Clinical Research; Professors D Kelleher, and P Murray from the Dublin Centre for Clinical Research; Eavan Daly and Cheryl Marron from GSK; Frank Keane and Enda Kelly from Vitalograph Ireland; the research staff of the Centres for Clinical Research at St Vincent's Hospital, Adelaide, Meath and National Children's Hospital (AMNCH), St James's Hospital and Cork University Hospital.

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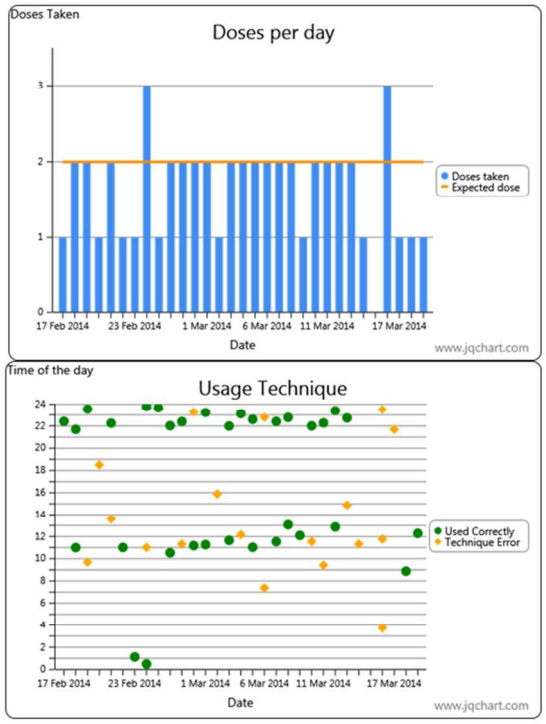

A screen shot of the data presented to the patient for discussion of their adherence to the salmeterol/fluticasone diskus inhaler over the prior month. In this example the patient has good time of use, in particular in the evening, suggesting they are developing a regular habit of use. However, they show intermittent errors in inhaler technique, in this example they used the inhaler incorrectly on almost half of all occasions in which the inhaler was used.
254x190mm (96 x 96 DPI)

Appendix 1

Inhaler Proficiency Schedule (IPS)

Patient ID: _____

Date: _____

Visit No: _____

	YES	NO
Does the patient hold the outer casing of the inhaler in one hand, whilst pushing the thumb grip away, until a click is heard?		
Does the patient hold the inhaler with mouthpiece towards himself?		
Does the patient slide lever away until it clicks?		
Does the patient hold the inhaler in a horizontal position?		
Does the patient breath out slowly and then put inhaler in front of mouth?		
Does the patient place mouthpiece between lips and breathe in as deeply as possible?		
Does the patient remove inhaler from mouth and hold breath for about 10 seconds?		
After 10 seconds does the patient breathe out slowly?		
Does the patient close the inhaler by sliding thumb grip back towards himself as far as it will go until it clicks?		
Does the patient gargle throat after use?		

Appendix 2

Clinical Training Manual

Including examples

Please note – throughout the manual, established behaviour change techniques are noted in parentheses, in accordance with the Behaviour Change Taxonomy (Michie et al., The Behavior Change Technique Taxonomy (v1) of 93 Hierarchically Clustered Techniques: Building an International Consensus for the Reporting of Behavior Change Interventions. Ann Behav Med 2013, 46: 81-95)

Summary

The "Best practice care" group

The principal themes of "Best practice care" group are:

1. Asthma education (nature of disease and need for treatment) and discussion on adherence, including-strategies to enhance adherence e.g. reminders and goal setting.

2. Training on inhaler use till proficient, as demonstrated with an Inhaler Proficiency Score (IPS, see appendix 2) observational score.

3. Advice on allergen or trigger avoidance; as related to PEFR.

The INCA group

The core features are listed:

1. The patient's treatment goal is established and used as the focus of the conversation. [This goal is to be referred to at each visit]

2. Data from the INCA device including (1) time of use, (2) pattern of using, to maximise habit forming (3) handling proficiency including inhalation flow rates are discussed, with graphs as shown in figure 2. These are aimed to enhance the value of the inhaler.

3. Data from the hand held PEFR, reliever use and AQLQ are correlated with the adherence so that these can be used to account for improvements or declines in these measures, to identify triggers

Screening visit/ Randomisation visit

Active and Control

"Tell me about your asthma and its treatment"

Opens the goals for treatment discussion, the rationale for treatment, and the inhaler technique.

All will have asthma explained as follows:

"Asthma is a clinical disease where the airways are irritated and swollen by dust, viruses, pollens and pollution. This irritation causes narrowing of the air passages which leads to you feeling tight, wheezy and short of breath" [5.1, 9.1]

All will have asthma treatment explained:

"Asthma is treated with an inhaler which has medicines which open the airways, to reduce the feelings of tightness and shortness of breath as well as a medicine which relieves the irritation, a steroid. The treatment that seems to work best is an inhaler that has two medicines, one to open the airways and the other lessens the inflammation and together they are very effective at treating most people's asthma. We think that using this type of medicine regularly helps keep you well"

"Any questions?"

"Are you happy with this explanation?"

Then:

"What would you say your goals for getting better are? List up to three, as specific as possible" [1.3].

Then:

At Visit 1 all participants (Active and Control) will demonstrate their INHALER TECHNIQUE and will be educated accordingly using the teach-to-goal approach. The IPS score after training will be recorded, **aiming** to reach 9/10. [6.1; 4.1].

Then:

All are shown how to use the PEFR meter [6.1.; 4.1].

At this visit, the physiological, clinical, past history and health status questionnaires are collected, see CRF.

Visits 2 to 4; every 4 weeks (21-30 days) for 12 weeks.

Control Group

Reviews progress over the last month

"How did you get on and how are you?"

"Have you been to the Doctor for your chest in the last month?"

Review of ACT, AQLQ peak flow measurements [2.2.;2.7.]

"How have you been getting on with your inhaler?"

This is an opportunity to promote strategies to encourage inhaler adherence e.g. try and identify some regular routine that the participant frequently does and tie in taking their inhaler at that time. For example "What time do you have dinner?" "Go to bed?" "Watch the news?" Link these to inhaler use. [7.1.;8.1.;8.3.]

INCA ACTIVE Group

"How did you get on and how are you?"

"Have you been to the Doctor for your chest in the last month?

Review of primary goals [1.7, possibly 1.6]. The old and the current ACT score is the focus of the discussion.

"What was it about your **asthma/health/goals** that you want to make better?"

"To achieve these aims need you to use your inhaler as best you can. It's really only after a few months of this that we can really see a big impact, eg changing/reducing your medication use."

"To get these goals, let us see if we can help you get the most from your inhaler."

Step 1 Doses/ timings graph (Figure 2). Focus on the positive aspects [2.7, 10.4]. For example "Well done you remember to take your inhaler most days ", or, "you are steady in the morning times, showing you have a good routine but the evening needs a little work". Try to identify some regular routine that the participant frequently does and tie in taking their inhaler at that time. For example "What time do you have dinner?" "Go to bed?" "Watch the news?" [7.1,8.1,8.3]. This is an opportunity to discuss barriers [1.2, possibly 12.1,

12.2] to regular inhaler use with the patient and for them to make suggestions on how they can link inhaler use with their asthma progress [5.1.;2.2].

Step 2. From the graphs, the errors are identified including exhalation, low peak inspiratory flow rates (peak inspiratory flow rate achieved on using the inhaler. If there was an error in handling the salmeterol/fluticasone inhaler this can be corrected using the teach-to-goal technique [4.1.]. If there are examples of low inspiratory flow then these are pointed out and further training, eg with the Clement Clark device is given. [2.2, 2.6]

Step 3 is the PEFR readings.–The day to day peak to trough variation and The weekly trend as well as (going up, staying the same, getting better) can then be related to the inhaler use, (going up, staying the same, getting better). [2.6.]

These data provide a point for the patient to discuss the outcomes in relation to their own life, e.g. if they were away, were in stressful situations, if they developed a URI, etc. [1.5]

Step 4. Inhaler reliever inhaler use. This is collected on the second INCA device, which is attached to a salbutamol inhaler. Note, the use of a reliever has been shown to be a good surrogate of adherence.

Step 5 combination graph where all the information on adherence, PEFR and symptoms are collated. These graphs provide a point for the patient to discuss reliever use in relation to their own life, eg if they were breathless, were in stressful situations [4.2], if they developed a URI, and if these coincide with PEFR changes or prior poor adherence [1.5] or if falling rates of inhaler use reflect increasing adherence to preventer therapy. This can be used as a reminder and a tool for discussing possible causes of exacerbations or loss of asthma control [1.5, 1.7].

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

A protocol for a randomised clinical trial of the effect of providing feedback on inhaler technique and adherence from an electronic device in poorly controlled severe asthma patients.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009350.R2
Article Type:	Protocol
Date Submitted by the Author:	21-Oct-2015
Complete List of Authors:	Sulaiman, Imran; Royal College of Surgeons Ireland, Respiratory Medicine MacHale, Elaine; Royal College of Surgeons Ireland, Respiratory Medicine Holmes, Martin; Trinity College Dubline, School of Bioengineering Hughes, Cian; Royal College of Surgeons Ireland, Respiratory Medicine D'Arcy, Shona; Trinity College Dubline, School of Bioengineering Taylor, Terence; Trinity College Dubline, School of Bioengineering Rapčan, Viliam; Trinity College Dubline, School of Bioengineering Doyle, Frank; Royal College of Surgeons Ireland, Respiratory Medicine Bhreathnach, Aoife; Royal College of Surgeons Ireland, Respiratory Medicine Seheult, Jansen; Royal College of Surgeons Ireland, Respiratory Medicine Murphy, Desmond; Cork University Hospital, Respiratory Medicine Hunt, Eoin; Cork University Hospital, Respiratory Medicine Lane, Stephen; Adelaide and Meath Hospital, Respiratory Medicine Sahadevan, Abhilash; Adelaide and Meath Hospital, Respiratory Medicine Crispino, Gloria; Royal College of Surgeons Ireland, Respiratory Medicine Diette, Gregory; The Johns Hopkins Hospital, Pulmonary Killane, Isabelle; Trinity College Dubline, School of Bioengineering Reilly, Richard; Trinity College Dubline, School of Bioengineering Costello, Richard; Royal College of Surgeons Ireland, Respiratory Medicine
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Communication, Medical education and training, Nursing, Patient-centred medicine
Keywords:	Adult thoracic medicine < THORACIC MEDICINE, Asthma < THORACIC MEDICINE, MEDICAL EDUCATION & TRAINING

A protocol for a randomised clinical trial of the effect of providing feedback on inhaler technique and adherence from an electronic device in poorly controlled severe asthma patients.

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Keywords
Severe asthma; adherence; INCA electronic monitor; Randomized controlled trial; inhaler technique.

Word Count: 3,430

Abstract

Introduction

In clinical practice it is difficult to distinguish between patients with refractory asthma from those with poorly controlled asthma, where symptoms persist due to poor adherence, inadequate inhaler technique or co-morbid diseases. We designed an audio recording device which, when attached to an inhaler, objectively identifies the time and technique of inhaler use, thereby assessing both aspects of adherence. This study will test the hypothesis that feedback on these two aspects of adherence to patients improves adherence and helps clinicians distinguish refractory from difficult to control asthma.

Methods

This is a, single blind, prospective randomized clinical trial performed at 5 research centers. Patients with partially controlled or uncontrolled severe asthma who have also had at least one severe asthma exacerbation in the prior year are eligible to participate. The effect of two types of nurse delivered education interventions to promote adherence and inhaler technique will be assessed. The active group will receive feedback on their inhaler technique and adherence from the new device over a three month period. The control group will also receive training in inhaler technique and strategies to promote adherence but no feedback from the device. The primary outcome is the difference in actual adherence, a measure that incorporates time and technique of inhaler use between groups at the end of the third month. Secondary outcomes include the number of patients who remain refractory despite good adherence, and differences in the components of adherence after the intervention. Data will be analyzed on an intention-to-treat and a per protocol basis. The sample size is 220 subjects (110 in each group) and loss to follow-up is estimated at 10% which will allow result to show a 10% difference (0.8 power) in adherence between group means with a Type I error probability of 0.05.

Registration: Clinicaltrials.gov NCT01529697

INTRODUCTION

Approximately 10% of patients with asthma remain poorly controlled with persisting symptoms and severe exacerbations despite use of combination therapy with long acting beta agonists and inhaled corticosteroids [1]. This poor control may be due to medication refractory asthma or due to difficult to manage asthma from issues such as poor inhaler technique, poor adherence or co-existing comorbid disease[1-3]. In practice distinguishing refractory from difficult to manage asthma is difficult. For example, adherence to medications, a particular problem in patients with severe asthma, is difficult to detect since self-report is unreliable [4]and pharmacy refill records only identify if the individual has collected a prescription. Some patients may demonstrate a reasonable inhaler technique when directly observed, but may be careless in their inhaler use on a day-to-day basis [5]. Hence, without objective longitudinal information on inhaler adherence and technique it is challenging to distinguish a patient with refractory asthma from one who has difficult to manage asthma [6]

We developed a device, INhaler Compliance Assessment device (INCA™), which makes a digital audio recording of an inhaler being used [5, 7-13]. Analysis of the audio recordings, by automated signal processing techniques, provides an objective assessment of both the time of inhaler use and the technique of inhaler use. Validation of the device and the audio recordings have been previously presented [5, 7-13]. We hypothesized that this information could be used both as part of an educational consultation for patients and for clinicians to help distinguish refractory from difficult to manage asthma.

The objective of this study is to assess if inhaler use obtained from the INCA™ device on time of use and technique of use leads to better inhaler adherence and better clinical information than current best practice.

METHODS

We describe the protocol of a randomised single blind, nurse delivered education study. The study will comprise of patients with severe asthma attending specialist hospital asthma clinics, who remain uncontrolled and have experienced at least one recent severe asthma exacerbation. Based on information obtained directly from the INCA™ acoustic recording device, one group (the active arm) will discuss patterns of adherence and training on technique of inhaler use. The second group (the control arm) will be given generalised strategies to improve adherence while technique errors will be corrected using checklists [14]. Adherence will be assessed objectively in all subjects.. Global outcomes will be quantified using the clinical, lung function, adherence and exacerbation data collected during the observation period.

Sponsorship

This is a researcher initiated study, funded by the Health Research Board of Ireland (HRB)(Pro/2011/57) and hosted within the Dublin Centre for Clinical Research (DCCR) clinical trials centres. The study sponsor, Royal College of Surgeons (RCSI), is an independent Medical University. The trial was approved by the Beaumont Hospital's Ethics committees. The trial is registered as NCT01529697 on Clinicaltrials.gov and a detailed statistical plan has been approved by an independent statistical team. The INCA™ device was manufactured and supplied by Vitalograph, Ennis, Ireland and GlaxoSmithKline provided the salmeterol/fluticasone diskus inhaler for this study.

Setting

This is a prospective, multi-centre, single blind randomized controlled trial of two nurse delivered strategies to optimise inhaler technique and adherence of patients with Stage 3 to 5 asthma. The study is being conducted at the Clinical Research Centres of five University Hospitals within the republic of Ireland (4 in Dublin County, 1 in Cork

County). At each centre between one and three nurses have been trained to provide either intervention. The lead clinical nurse was educated by the principal investigator and a respiratory nurse specialist. All other nurses were educated by our lead clinical nurse in a teach to goal method with demonstration. The study period is from 2011 with ongoing recruitment.

Participants (n=220)

Prior to study recruitment an asthma diagnosis is made using a clinician diagnosis supported by one or more of the -following: obstructive spirometry with a minimum of10% reversibility, either spontaneously over time or with inhaled beta agonist or with a minimum 15% peak flow variability over time or through a positive bronchial provocation challenge.

Inclusion criteria

Patients already prescribed therapy equivalent to step 3 or higher on the Asthma Management Guidelines (1) for at least 3 months and who had at least one exacerbation treated with systemic glucocorticoids in the prior year and who are either uncontrolled or partially controlled by GINA guidelines are eligible for inclusion [1]. Patients must also be 18 years or older in age.

Exclusion criteria

Patients who are controlled, as defined by the GINA criteria [1] on their current therapy. Additional exclusion criteria are those who are unwilling to participate in a clinical study, current smokers or prior hypersensitivity to salmeterol/ fluticasone. There are no other exclusion criteria.

Study design

The study flow is indicated in Table 1.

Study Procedure	Visit 1	Visit 2	Visit 3	Visit 4
Informed Consent	X			
Demographics	X			
Medical History	X			
Inclusion & exclusion Criteria	X			
Current medications	X			
Physical Examination	X			X
Vital signs	X	X	X	X
AQLQ	X	X	X	X
ACT	X	X	X	X
Randomisation	X			
Dispense adapted Seretide inhaler	X	X	X	
Dispense electronic PEFR monitor	X	X	X	
Download device readings active only		X	X	X
Inhaler use education	X	X	X	X
Adverse events Recorded		X	X	X
Concomitant medications Recorded		X	X	X

Table 1: Details of Study data collection The Active group receive a copy of device readings and active feedback about adherence and inhaler technique, Visit 1:

Screening Visit: at time of enrolment (Week 0); Visit 2: at end of month one (Week 4); Visit 3: at end of month two (Week 8); Visit 4: Final Visit at the end of month three (Week 12). AQLQ = Asthma Quality of Life Questionnaire, ACT= Asthma Control Test, PEFR= Peak Expiratory Flow Rate

Patients identified at specialist asthma clinics who meet the inclusion and not the exclusion criteria are invited to participate in the study. Once consented each study visit is performed by a registered nurse.

The dose of inhaled corticosteroid and Long Acting Beta-Agonist (LABA) is not changed at recruitment and during the study procedure, as the main aim of the study is to improve adherence to current asthma treatment.

The audio recording technology has not yet been established for the turbohaler or the pMDI, hence, for those participants who are currently prescribed formoterol/budesonide/beclomethasone, at recruitment, their therapy is changed to an equivalent dose of salmeterol/fluticasone delivered via a diskus device. This change is made by the physician looking after the patient in the outpatient clinic. Following this the patient is then referred to the study. The patient may still refuse to enter the study. All other aspects of regular patient care are continued.

At the initial visit the participant's age, sex, height, weight, duration of asthma, smoking history, number of courses of steroids in the prior year are recorded (self-reported by the participant). The dose of salmeterol/fluticasone and duration of taking this dose, use and dose of other inhaled therapy including short acting beta agonists, Long Acting Muscarinic Antagonist (LAMA), nasal steroid and antihistamines are recorded. The

nurse records the Peak Expiratory Flor Rate (PEFR) and an Inhaler Proficiency checklist Score (IPS; Appendix 1), a ten point checklist score. The Asthma Control Test (ACT) score and Asthma Quality of Life Questionnaire (AQLQ) (15)are completed by the participant. Serum total and specific immunoglobulin E levels and peripheral blood eosinophil levels, prior spirometry and bronchial provocation test are recorded from the clinical notes.

The participants receive a salmeterol/fluticasone diskus inhaler with an INCA™ device attached and they are asked to use the inhaler twice per day and to take reliever salbutamol, as required, for break through symptoms. All participants are informed at recruitment that the device would provide information on how and when they use their inhaler. Participants are asked to record their peak expiratory flow with an electronic monitor (ASMA-1, Vitalograph, Ennis, Ireland) twice daily.

Visits are scheduled 4, 8 and 12 weeks later, summarised in Figure 1. At these, the participants return their inhaler and electronic Peak flow monitor. Additionally, at each of these visits the ACT, AQLQ, PEFR as well as any exacerbations and changes in medications, including new medications are recorded. Due to an omission in the original study protocol, where ACT was not a measured variable, ACT has not been recorded on the first 60 participants. The training, as per allocation, is then given. Details of the clinical visits are included in the clinical training manual, Appendix 2.

Interventions

Control group: Behavioural intervention and inhaler training

The key points of each of the visit consultations includes; participant identified goals for outcomes, exploration of barriers to achieving goals, explanation of the purpose of asthma treatment and provision of an asthma management plan for exacerbations. A

checklist is used to review and correct errors in inhaler technique (IPS). To promote adherence during the education emphasis is given on the individual developing a habit in time of use of the inhaler. Four, 8 and 12 weeks later the participants return their inhaler and receives an identical structured consultation as at the first meeting. Participants and nursing staff are unaware of data from the INCA device in the control arm. A video and manual describing the exact steps of usual care is shown as https://www.youtube.com/watch?v=PlTkhVuogaI

Active group: Feedback using recordings from the INCA Device

The content of the first visit was the same as for the control group. At the four, eight and twelve weeks later the participants together with the nurse review the information recorded on the INCA device and electronic PEFR, in the form of a graph, see Figure 2 for an example of graphs produced by the INCA device. This graph leads to a consultation that focuses on the time of use, patterns of inhaler use attempting to identify barriers to good adherence, development of habit of use as well as remediation of errors of inhaler use, as identified by the analysis the data.

Data collection

The INCA Device

The original INCA™ device was designed at the Department of Bioengineering, TCD, Ireland and CE marked and manufactured by Vitalograph, Ennis, Ireland.

Analysis of the audio data

Analysis of the digital recordings are performed as previously described [5]. The files are uploaded to a server and analysed using signal processing methods. For patients in the active arm, these audio recordings are uploaded during the visit by the nurse and

feedback is given to the patient based on an automated analysis of the audio files. The sensitivity and specificity details have been published [7].

At a later date two independent raters over-read all files from all patients. Their agreed, combined analysis will be used in the calculation of the actual adherence. These raters are unaware of either the patient allocation or any of the patient clinical outcomes and are not involved in any aspect of the patient care during the trial. Critical inhaler errors including whether the drug was primed, whether the patient exhaled after priming but before inhalation, whether an adequate flow rate was achieved, the exact flow rate, whether there were multiple inhalations indicating inadequate breath-holds and correct sequence of events/timing of events were performed. Non-critical errors such as not holding the device vertically (as described by the manufacturer) were not recorded. The sensitivity and agreement within the two raters and between the raters and the algorithm have been published [9] . Any disagreements within raters were reviewed by a third rater who made the final decision on the audio file.

Electronic Peak Expiratory Flow Rate (ePEFR)

Participants receive an ePEFR device at each visit, which are then collected at the subsequent visit. For participants in the active arm, data from these devices are downloaded during the visit and information on PEFR, in conjunction with adherence data from the INCA device, are feedback to the participant.

Objectives

The objective of this study is to assess if feedback obtained from the INCA™ device on adherence and technique errors yields better adherence and better clinical information than best practice.

Primary outcome

The actual inhaler adherence, expressed as cumulative drug exposure, is calculated by combining the time of use along with the interval between doses (correct time is twice a day, in a period not less than 6 hours between the last dose and the subsequent dose or at a time greater than 18 hours apart from the previous dose.) and incorporating, by audio analysis, if the inhaler was used correctly (ie. no evidence of critical technique errors mentioned above). The rate of actual adherence for the last month of the intervention will be compared between the active and control patients.

Secondary outcome analysis will include:

Clinical outcomes, PEFR, ACT, AQLQ, reliever use and exacerbations between active and control arms at the end of the study will be compared. A composite score of these values, the global clinical outcome profile, see Table 2 comprising the observed adherence, peak flow data, asthma control, quality of life and reliever use as well as, exacerbations over the study period will be calculated. Exacerbations is defined as an increase in symptoms (ie shortness of breath, wheeze, cough) requiring a course of systemic glucocorticoids. Healthcare utilisation (ie. unscheduled GP visits, hospitalization and emergency department visits) will also be compared between active and control arms.

	Non-adherence	Refractory Asthma	Controlled Asthma	Co-morbidity
Actual adherence > 80%	No	Yes	Yes or No	Yes
PEFR >80 of Area Under the Curve (AUC)	Yes or No	No	Yes	Yes
AQLQ >5 and ACT >19	Yes or No	No	Yes	No

Exacerbations	Yes or No	Yes or No	No	Yes or No

Table 2: Clinical Decision tool. The outcome decision tool, at the end of the study the cumulative information on actual adherence, PEFR rate, calculated as the AUC within 80% of normal predicted, ACT and AQLQ considered to be optimal and exacerbations will be used to describe one of four possible outcomes; sufficiently non-adherent as the likely reason for failure to progress, asthma that is refractory because despite optimal adherence both symptoms and lung function and exacerbations occur, controlled asthma, patients in whom there are no longer impaired nor have exacerbations, and a group of patients who have good adherence and lung function but who continue to have symptoms therefore suggesting that a significant co-morbidity is likely driver for the ongoing symptoms.

Comparison of the proportion of patients in each group who achieved full adherence at the end of the study (≥80%), as well as changes in patterns of adherence in the two groups, the number progressing to good actual technique will be assessed. A comparison of the morning and evening habit of inhaler use, error rates, overdose rates, interval and attempted rates of adherence in the two groups at the end of the study will be compared. The factors associated with improving adherence will be described.

The relationship between adherence and asthma control, asthma quality of life and PEFR will be assessed by comparing the proportion of patients who are GINA 2011, ACT controlled and are no longer requiring regular beta agonist. The ACT, PEFR rate, AQLQ and reliever use between the two groups will also be compared.

The Kappa score between raters and a sensitivity analysis of the algorithm will be calculated.

Sample size calculation

The usual rate of adherence to inhalers is reported to be calculated from dose counter and is expressed as an average adherence. Most studies in trials of patients with inhalers report adherence of >0.8. Therefore, we anticipate that there is going to be high adherence in the setting of a clinical trial. However, we also expect that there will be a number of patients with poor inhaler technique which will lead to a lower actual adherence. We shall assume that when this is accounted for then the actual adherence is 0.15 lower, ie: 0.65 adherence at the end of the first month. Our preliminary data in primary care and on the wards indicates a standard deviation of adherence is 0.25 [5]. The primary endpoint is the rate of adherence at the end of the study period, ie: during the last visit at month three between active and control groups. We expect the adherence to improve over the study period in the control group, as they are repeatedly educated in inhaler use by 0.05 and we expect the active group to get closer to the physician reported ideal rate of 0.8, i.e. a 0.15 improvement in actual adherence. Hence, with a power of 0.8 at the 0.05 significance level, with a 0.1 difference in the actual adherence rate then a sample size of 100 in each limb is required. We expect a 10% dropout; hence the target recruitment sample size is 220 in total.

Randomisation and allocation.

Randomisation will use a stratified by site random block design, with blocks varying in size of 8-12. Allocation Ratio is 1:1 with a central computer generated randomisation. This is a single blind study, the nurse may deliver either intervention and is not blinded to the allocation. The participants are aware which group they are

allocated to and aware that data on adherence is being collected for analysis. Patients in the control arm will be blinded to their adherence data from the INCA™ device.

Statistical Methods

Data analysis

Data will be analyzed on an intention-to-treat and a per protocol basis. Data will be presented as means with standard deviations and Student's t test will be used to compare differences in mean adherence rates between the groups. Significance will be set at the 5% level. Stratification of patients by new versus previous use with respect to use of the Diskus device (ie. if patient's are using the Diskus device for the first time, or if they have previously used the device), stratification based on severity of disease according to GINA guidelines.

Discussion

Most management guidelines suggest that for poorly controlled asthma patients that before changing therapy, issues with adherence and inhaler technique need to be addressed [1-3]. However, this is difficult to achieve in clinical practice. The aim of this study is to see if a nurse delivered educational intervention with repeated education and monitored adherence can improve both aspects of adherence, the time and the technique of inhaler use. We will record when and how well an individual has used their inhaler over time with a device that makes a digital audio recording of an individual using their inhaler. Analysis of the recorded time of use, the interval between use and technique of use provides a measure termed actual adherence. The study's primary outcome will be a comparison of the actual adherence between the two groups, at the end of the third month of participation in the study.

It is expected that over the study period some patients will become fully controlled. while others will remain poorly controlled despite being fully adherent over the study period and others may remain uncontrolled but also poorly adherent. This information may help with clinical decision making for individual patients for example by helping decide whom should have their therapy increased, their inhaler device changed or further interventions to promote adherence such as motivational interviewing Hence, by combining clinical outcomes with the longitudinally collected adherence, asthma control and PEFR data, the composite outcome may assist a clinician in identifying the cause of difficult to manage asthma and increase the clinical confidence that the patient has refractory asthma.

This study has several novel features; this is the first to use a technology that objectively assesses adherence to inhalers both in terms of technique of use as well as time of use. This technology involves not simply the device but also the automated algorithms, the feedback tools and the content of the feedback delivered by the nurse during the consultation.

It could be argued that the results of this clinical research study, performed in a research setting, will lead to greatly improved adherence, which is not reflective of clinical practice. Additionally both control and active patients will be reviewed on a monthly basis for three months. This approach itself will more than likely also lead to an increase in adherence in the active and control group and may not fully reflect 'usual care.' To add to this patients in both the active and control arm are aware that their inhaler use is being 'monitored' and this may lead to increased inhaler adherence. The authors see no alternative way of performing the study as practical challenges in a more real world setting may lead to a significant loss of patient follow up and hence less precise information. The benefits of regular visits and PEFR measurements outweigh the disadvantages. Another limitation of the study is that it has a limited follow up time frame, hence the long-term effect on clinical outcomes and persistence of the observed benefits will not be established.

In regards to safety, patients enrolled in this study have to be uncontrolled or partially controlled by GINA guidelines. However, for the duration of the study their regular medical treatment of their asthma will not be changed (ie. their ICS/LABA dose will remain unchanged). The rationale behind this, is to see the effect three months of adherence training would have on asthma control, potentially reducing the need to increase patient medication (step-up) and possibly allowing physicians to reduce

asthma treatment (step-down). Patients can withdraw at any time during the study without any impact on their clinical care. Additionally if the clinician feels there is a clinical indication, patients can be removed from the study for the patient's best interest.

In summary, this study proposes to assess the impact of a series of consecutive education visits on adherence and inhaler use by patients with severe asthma. In addition by combining objective measurement of lung function, clinical outcomes and objectively assessed adherence this may also provide clinicians greater precision in decision making for the future care of this group of patients.

Abbreviations

ACT; asthma control test, AQLQ; asthma quality of life score, INCA; inhaler compliance aid, PEFR; peak expiratory flow rate. IPS; inhaler proficiency score.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RR, CH and RC conceived the INCA device. RC conceived and designed the study. EMacH, IS, GD, SD and MF each made substantial contributions to study design; JS, MH, TT, IS, SD, IK, WR have all been involved in defining the characteristics of the INCA device and the associated acoustic and other analysis. GC provided the statistical support and contributed to the drafting of the manuscript. All authors were

involved in the writing of the manuscript and revising it critically for intellectual content; and have given final approval of the version to be published. All authors read and approved the final manuscript.

Acknowledgements

This study is funded by the Health Research Board of Ireland. The authors would like to thank Deidre Hyland, John McCourt and D Kenny RCSI Centre for Clinical Research; Professors D Kelleher, and P Murray from the Dublin Centre for Clinical Research; Eavan Daly and Cheryl Marron from GSK; Frank Keane and Enda Kelly from Vitalograph Ireland; the research staff of the Centres for Clinical Research at St Vincent's Hospital, Adelaide, Meath and National Children's Hospital (AMNCH), St James's Hospital and Cork University Hospital.

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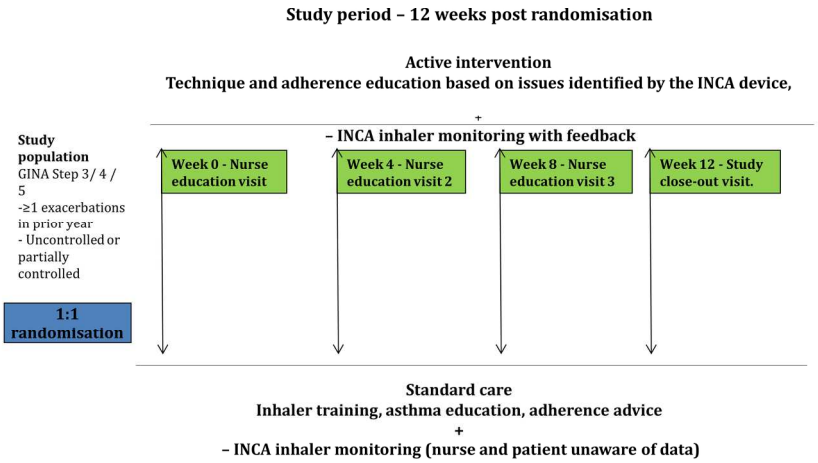
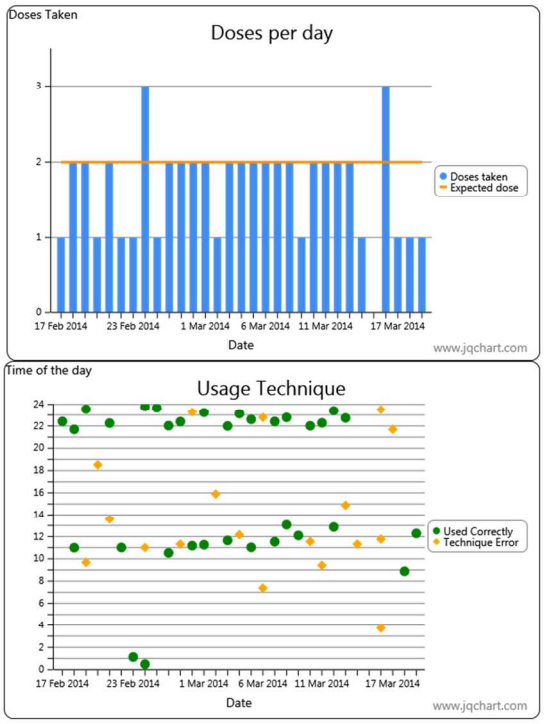


The study participants are patients with a diagnosis of asthma attending a severe asthma clinic who remain uncontrolled or partially controlled and have experienced at least one severe exacerbation of asthma in the prior year. With no medication change adherence and inhaler technique are re-enforced over the 12 week monitoring period.
190x142mm (300 x 300 DPI)



A screen shot of the data presented to the patient for discussion of their adherence to the salmeterol/fluticasone diskus inhaler over the prior month. In this example the patient has good time of use, in particular in the evening, suggesting they are developing a regular habit of use. However, they show intermittent errors in inhaler technique, in this example they used the inhaler incorrectly on almost half of all occasions in which the inhaler was used.
190x142mm (300 x 300 DPI)

Appendix 1

Inhaler Proficiency Schedule (IPS)

Patient ID: _____

Date: _____

Visit No: _____

	YES	NO
Does the patient hold the outer casing of the inhaler in one hand, whilst pushing the thumb grip away, until a click is heard?		
Does the patient hold the inhaler with mouthpiece towards himself?		
Does the patient slide lever away until it clicks?		
Does the patient hold the inhaler in a horizontal position?		
Does the patient breath out slowly and then put inhaler in front of mouth?		
Does the patient place mouthpiece between lips and breathe in as deeply as possible?		
Does the patient remove inhaler from mouth and hold breath for about 10 seconds?		
After 10 seconds does the patient breathe out slowly?		
Does the patient close the inhaler by sliding thumb grip back towards himself as far as it will go until it clicks?		
Does the patient gargle throat after use?		

Appendix 2

Clinical Training Manual

Including examples

Please note – throughout the manual, established behaviour change techniques are noted in parentheses, in accordance with the Behaviour Change Taxonomy (Michie et al., The Behavior Change Technique Taxonomy (v1) of 93 Hierarchically Clustered Techniques: Building an International Consensus for the Reporting of Behavior Change Interventions. Ann Behav Med 2013, 46: 81-95)

Summary

The "Best practice care" group

The principal themes of "Best practice care" group are:

1. Asthma education (nature of disease and need for treatment) and discussion on adherence, including-strategies to enhance adherence e.g. reminders and goal setting.

2. Training on inhaler use till proficient, as demonstrated with an Inhaler Proficiency Score (IPS, see appendix 2) observational score.

3. Advice on allergen or trigger avoidance; as related to PEFR.

The INCA group

The core features are listed:

1. The patient's treatment goal is established and used as the focus of the conversation. [This goal is to be referred to at each visit]

2. Data from the INCA device including (1) time of use, (2) pattern of using, to maximise habit forming (3) handling proficiency including inhalation flow rates are discussed, with graphs as shown in figure 2. These are aimed to enhance the value of the inhaler.

3. Data from the hand held PEFR, reliever use and AQLQ are correlated with the adherence so that these can be used to account for improvements or declines in these measures, to identify triggers

Screening visit/ Randomisation visit

Active and Control

"Tell me about your asthma and its treatment"

Opens the goals for treatment discussion, the rationale for treatment, and the inhaler technique.

All will have asthma explained as follows:

"Asthma is a clinical disease where the airways are irritated and swollen by dust, viruses, pollens and pollution. This irritation causes narrowing of the air passages which leads to you feeling tight, wheezy and short of breath" [5.1, 9.1]

All will have asthma treatment explained:

"Asthma is treated with an inhaler which has medicines which open the airways, to reduce the feelings of tightness and shortness of breath as well as a medicine which relieves the irritation, a steroid. The treatment that seems to work best is an inhaler that has two medicines, one to open the airways and the other lessens the inflammation and together they are very effective at treating most people's asthma. We think that using this type of medicine regularly helps keep you well"

"Any questions?"

"Are you happy with this explanation?"

Then:

"What would you say your goals for getting better are? List up to three, as specific as possible" [1.3].

Then:

At Visit 1 all participants (Active and Control) will demonstrate their INHALER TECHNIQUE and will be educated accordingly using the teach-to-goal approach. The IPS score after training will be recorded, **aiming** to reach 9/10. [6.1; 4.1].

Then:

All are shown how to use the PEFR meter [6.1.; 4.1].

At this visit, the physiological, clinical, past history and health status questionnaires are collected, see CRF.

Visits 2 to 4; every 4 weeks (21-30 days) for 12 weeks.

Control Group

Reviews progress over the last month

"How did you get on and how are you?"

"Have you been to the Doctor for your chest in the last month?"

Review of ACT, AQLQ peak flow measurements [2.2.;2.7.]

"How have you been getting on with your inhaler?"

This is an opportunity to promote strategies to encourage inhaler adherence e.g. try and identify some regular routine that the participant frequently does and tie in taking their inhaler at that time. For example "What time do you have dinner?" "Go to bed?" "Watch the news?" Link these to inhaler use. [7.1.;8.1.;8.3.]

INCA ACTIVE Group

"How did you get on and how are you?"

"Have you been to the Doctor for your chest in the last month?

Review of primary goals [1.7, possibly 1.6]. The old and the current ACT score is the focus of the discussion.

"What was it about your **asthma/health/goals** that you want to make better?"

"To achieve these aims need you to use your inhaler as best you can. It's really only after a few months of this that we can really see a big impact, eg changing/reducing your medication use."

"To get these goals, let us see if we can help you get the most from your inhaler."

Step 1 Doses/ timings graph (Figure 2). Focus on the positive aspects [2.7, 10.4]. For example "Well done you remember to take your inhaler most days ", or, "you are steady in the morning times, showing you have a good routine but the evening needs a little work". Try to identify some regular routine that the participant frequently does and tie in taking their inhaler at that time. For example "What time do you have dinner?" "Go to bed?" "Watch the news?" [7.1,8.1,8.3]. This is an opportunity to discuss barriers [1.2, possibly 12.1,

12.2] to regular inhaler use with the patient and for them to make suggestions on how they can link inhaler use with their asthma progress [5.1.;2.2].

Step 2. From the graphs, the errors are identified including exhalation, low peak inspiratory flow rates (peak inspiratory flow rate achieved on using the inhaler. If there was an error in handling the salmeterol/fluticasone inhaler this can be corrected using the teach-to-goal technique [4.1.]. If there are examples of low inspiratory flow then these are pointed out and further training, eg with the Clement Clark device is given. [2.2, 2.6]

Step 3 is the PEFR readings.–The day to day peak to trough variation and The weekly trend as well as (going up, staying the same, getting better) can then be related to the inhaler use, (going up, staying the same, getting better). [2.6.]

These data provide a point for the patient to discuss the outcomes in relation to their own life, e.g. if they were away, were in stressful situations, if they developed a URI, etc. [1.5]

Step 4. Inhaler reliever inhaler use. This is collected on the second INCA device, which is attached to a salbutamol inhaler. Note, the use of a reliever has been shown to be a good surrogate of adherence.

Step 5 combination graph where all the information on adherence, PEFR and symptoms are collated. These graphs provide a point for the patient to discuss reliever use in relation to their own life, eg if they were breathless, were in stressful situations [4.2], if they developed a URI, and if these coincide with PEFR changes or prior poor adherence [1.5] or if falling rates of inhaler use reflect increasing adherence to preventer therapy. This can be used as a reminder and a tool for discussing possible causes of exacerbations or loss of asthma control [1.5, 1.7].

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.