RESEARCH PROTOCOL

ASSIST Study:

ASsessment of an electronic System and the Impact on Inhaler Skills and Technique

Contents

1 RESEARCH TEAM & KEY CONTACTS

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2 INTRODUCTION

Asthma is one of the most common chronic diseases and is typically treated using pressurised metered dose inhalers (pMDIs). However, it is estimated that around 90% of people make errors

when using these, leading to poor symptom control and risks of serious asthma attacks as well as side-effects and medication overuse [1]. The Clip-Tone System (CTS) is a small device fitted to the top of the patients' inhaler which emits a specific sound with optimal inhaler use, that is detected by an accompanying mobile application (app) which provides real-time feedback to patients to improve their technique.

Aims and objectives

This study aims to evaluate the impact of the Clip-Tone Buddy and app (Clip-Tone System; CTS) on improving the proficiency of inhaler use by patients and potential subsequent impact on their asthma control.

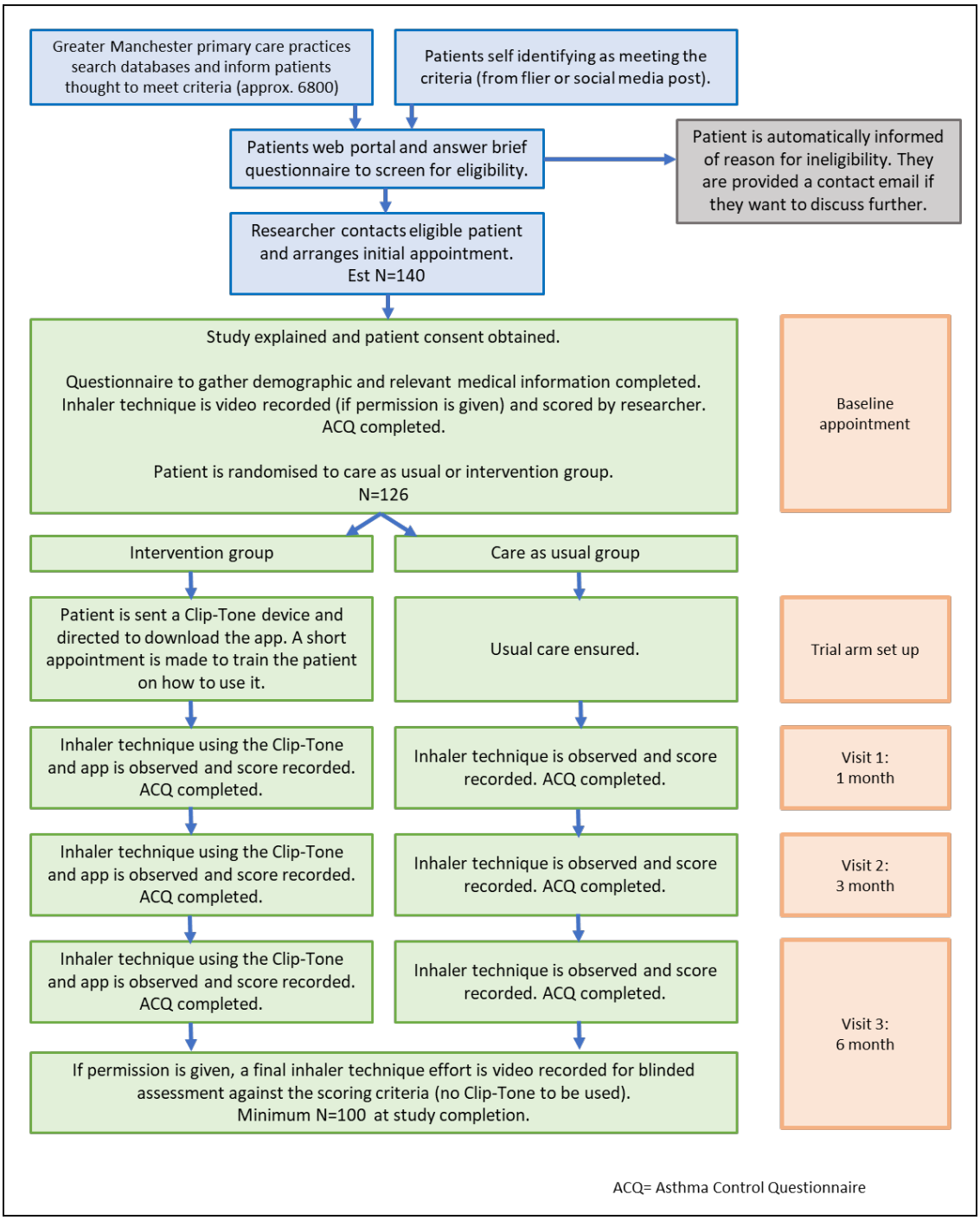
Methods

This study involves a randomised controlled trial of the use of the CTS versus usual care in patients with asthma who are using pMDI devices. Participants will be primary care patients aged 16 years and over who are prescribed regular pMDI medication for asthma. After standard inhaler technique and asthma assessment, each of the participants will be randomised to either receive care as usual or to receive the CTS. All patients will be followed up remotely at 1 month, 3 months and 6 months following enrolment. At each follow-up, inhaler technique will be assessed and scored using the validated UK inhaler group checklist, asthma control questionnaire (ACQ5) completed and any relevant unscheduled GP or hospital visits recorded. To show a difference of 30% in the proportion of participants with the correct inhaler technique at follow-up (Power=0.9, P=0.05), a sample size of 126 participants (63 per group), will be recruited allowing for a 20% drop-out rate. Secondary objectives of this study are dedicated towards developing understanding of how patients perceive use of Clip-Tone System in a real-world setting. A health economic assessment of the data will also take place.

Dissemination and Impact

The outputs of the research will be published in a peer reviewed journal and presented at national and international conferences. Results will be disseminated to participants.
The planned research is intended to produce evidence to support the broad intended purpose of the CTS. It will allow for benefits to be understood and highlighted to users and potential customers.

The flow chart below summarises the study plan.


Greater Manchester primary care practices search databases and inform patients thought to meet criteria (approx. 6800)
Patients self identifying as meeting the criteria (from flier or social media post).
Patients web portal and answer brief questionnaire to screen for eligibility.
Patient is automatically informed of reason for ineligibility. They are provided a contact email if they want to discuss further.
Researcher contacts eligible patient and arranges initial appointment. Est N=140
Study explained and patient consent obtained.
Questionnaire to gather demographic and relevant medical information completed. Inhaler technique is video recorded (if permission is given) and scored by researcher. ACQ completed.
Patient is randomised to care as usual or intervention group. N=126
Baseline appointment
Intervention group
Care as usual group
Patient is sent a Clip-Tone device and directed to download the app. A short appointment is made to train the patient on how to use it.
Usual care ensured.
Trial arm set up
Inhaler technique using the Clip-Tone and app is observed and score recorded. ACQ completed.
Inhaler technique is observed and score recorded. ACQ completed.
Visit 1: 1 month
Inhaler technique using the Clip-Tone and app is observed and score recorded. ACQ completed.
Inhaler technique is observed and score recorded. ACQ completed.
Visit 2: 3 month
Inhaler technique using the Clip-Tone and app is observed and score recorded. ACQ completed.
Inhaler technique is observed and score recorded. ACQ completed.
Visit 3: 6 month
If permission is given, a final inhaler technique effort is video recorded for blinded assessment against the scoring criteria (no Clip-Tone to be used). Minimum N=100 at study completion.
ACQ= Asthma Control Questionnaire

3 BACKGROUND

Asthma is one of the most prevalent chronic diseases – with 5.4million people receiving treatment in the UK [2] and 300million worldwide[3]. The mainstay of treatment is with inhaled medication. The advantage of administering medication by inhaler is that it is delivered directly to the airways, allowing rapid onset of action and minimising systemic side effects [4]. This medication can be highly effective, if taken correctly. However, it is estimated that around 90% of people make errors when using pressurised metered dose inhalers (pMDIs), the most common inhaler device used [5]. In addition to poor inhaler technique amongst patients, evidence shows healthcare professionals (HCPs) themselves make frequent errors and therefore are not always capable of demonstrating ideal technique to patients [6]. Using the correct technique can improve asthma symptoms, reduce risks of serious asthma attacks and reduce side effects and overuse of medication [1]. There is currently no objective method of assessing inhaler technique or an opportunity for patients to re-check their own technique. The proposed study aims to evaluate the use of a new inhaler technique self-management tool to assess the longer-term impact on proficiency of inhaler use and subsequent impact on disease control.

As asthma medication is predominantly given by inhaler, it is not surprising that inhaler technique errors have been linked with poor disease control [7]. Consequently, poor inhaler technique has been shown to lead to an increased risk of hospitalisation, A+E visits and oral steroid use [8]. In fact, inhaler technique review was one of a number of key recommendations in the National Review of Asthma Deaths [9]. As well as poor control, inadequate inhaler technique has resulted in increased side effects due to greater systemic absorption and patients requiring higher dose medications. Uncontrolled disease can impact patients' quality of life, and have indirect economic impacts through, for example, lost workdays affecting society as a whole [10]. The NHS long term plan (www.longtermplan.nhs.uk) lists respiratory care as a top priority, citing the fact admissions for respiratory disease have risen at 3 times the rate of admissions generally. Overall, asthma costs the UK health service at least £1.1billion each year, and around £666millon of this is spent on prescriptions [11], with similar impacts seen globally. By addressing this significant problem, and allowing patients to independently check their inhaler technique, some of these avoidable costs can be mitigated without compromising care.

<u>Existing literature supports the need for inhaler technique assessment.</u>

NICE guidelines [12] on monitoring asthma control include frequent inhaler technique checks, at annual reviews, at every consultation following an asthma attack and whenever a new inhaler is prescribed. It also recommends that review opportunities are identified in community pharmacies. These checks involve subjective observation following demonstration by the HCP in the clinic setting and/or access to videos demonstrating optimal device use. However, despite these guidelines and resources, evidence shows that the situation has not changed in the last 40 years [13] and studies on inhaler technique have demonstrated that once trained and assessed as competent, patients' technique frequently wanes over time and training needs repeating regularly

[14]. In a recent document drawn up by the British Thoracic Society, review of inhaler technique was one of five elements highlighted as an action most likely to improve patient care [15]. However, many of these opportunities are lost due to lack of time and/or trained staff. Of note, many patients actively seek self-management opportunities, with a recent Asthma UK survey revealing that 93% of patients would welcome the use of apps to collect data to facilitate their interactions with their HCP [16].

Providing an effective method of reinforcing inhaler technique in the home setting on a regular basis, will help embed good habits. Reducing errors can improve clinical outcomes including disease control and fewer hospital admissions [1]. The use of the technology to be assessed here, Clip-Tone (Clement Clarke International, UK - collaborator) and the Clip-Tone Buddy app (Clin-e-cal Ltd, UK – lead applicant) is designed to provide exactly this support. Together these are known as the Clip-Tone System, CTS.

Technology summary

Clip-Tone is a small device fitted to the top of the patients' inhaler. It is designed to emit a specific frequency of sound when the flow rate through the inhaler matches that of optimal technique. If inhalation speed fluctuates outside the ideal flow rate during the inhalation event, the whistle sound will stop or change. The Clip-Tone Buddy app identifies this specific sound frequency and provides real time feedback on inhalation length, and the timing of the sound of the actuation (canister press). When the inhalation has ceased an assessment of the users' technique will be displayed on the app, and tips to improve will be provided helping the patient master an effective technique.

The intended purpose of Clip-Tone Buddy is to guide inhaler technique and is a class I medical device accessory and tier 2 digital health technology, according to the digital evidence standards framework.

Supporting evidence for the use of the technology

Clin-e-cal's Sound Response technology is a software engine which identifies and responds to tones and sounds emitted by respiratory devices. To date the company has developed a successful app (Rafi-Tone) aimed at young children using inhalers with a spacer. This uses gamification techniques to engage and encourage the child [17]. Additionally, Clin-e-cal has developed a training app, Trainhaler Buddy, designed to help HCPs and patients develop appropriate inhalation flow and length. A study of 371 patients allocated to verbal counselling alone or verbal counselling with use of the Trainhaler Buddy found that patients trained using the app had a significant improvement in achieving the correct inhaler technique and also a significant early improvement in lung function and asthma control score, compared with the control group [18].

The Clip-Tone Buddy app has been built on this technology; developing a user-friendly app giving real-time inhaler technique feedback to optimise pMDI drug delivery. A preliminary study demonstrated that the deep and slow inhalation technique required when using a pMDI was improved in those using both the visual and audio feedback given with the Clip-Tone system

compared to verbal counselling alone [19]. Additionally, a small group of users have assessed the app for usability, informing the design and the development of the user interface and algorithm sensitivity.

The Clip-Tone System (CTS) can facilitate training when patients are first introduced to an inhaler and reinforce effective inhaler use whenever they use the device, embedding effective habits. The CTS is currently compatible with 90% of pressurised metered dose inhaler (pMDI) type inhalers prescribed in the UK (and pMDIs represent approximately 70% of UK inhaler prescriptions). The study described will examine the impact of the CTS on handling errors by assessing the inhaler technique score at 1, 3 and 6 months. As a secondary outcome, we will also examine the impact on asthma control. This will provide evidence that the CTS can address the long standing issue of inhaler technique which can be used in a health economic assessment to help drive uptake and adoption.

Funding
This study has been awarded funding from an NIHR i4i Product Development Award. This is a collaborative application between the University of Manchester and Clin-e-cal Ltd (the Clip-Tone Buddy app developer). The grant reference is: 202884.

4 STUDY OBJECTIVES

4.1 Primary Question/Objective:

The primary objective of the study is to answer the question: “Does use of the Clip-Tone System help people achieve and maintain effective inhaler technique for at least 6-months compared to those receiving care as usual?”.

4.2 Secondary Question/Objective:

Secondary questions that will be investigated with the data collected are:

“Do patients using the CTS have improved asthma control compared to those receiving care as usual?”

“Do patients using the CTS more frequently make fewer inhaler technique errors than those using it less frequently?”

5 STUDY DESIGN & PROTOCOL

5.1 Participants

The study will recruit 126 participants. These will be randomised into a care as usual group and an intervention group.

Participants will be over the age of 16 and will have a current asthma diagnosis. They will be currently prescribed one of the relevant inhalers (see section: 6.1).

5.2 Study Intervention and/or Procedures

The main aim of the study is:
To establish whether the use of the Clip-Tone System (CTS) improves and maintain inhaler technique in asthmatic patients (> 16 years) over a 6-month period compared with those receiving "usual care" alone.
Other aims include:
To assess the use of the CTS in asthmatic patients (> 16 years) and its effects on asthma control and
unscheduled clinical visits over a period of 6-months
To develop understanding of how patients use CTS in a real-world setting.
To develop understanding of what frequency of use of CTS is desirable.

The technology: Clip-Tone System
The technology consists of two parts:
1) Clip-Tone - a small plastic retrofit device available in two variants (developed and manufactured by commercial partner Clement Clarke International; both CE marked, Class I medical devices available on prescription from May 2021) (See Figure A, Appendix 1)
a) Clip-Tone E fits GSK manufactured Evohalers (Ventolin, Flixotide, Seretide brands)
b) Clip-Tone F fits Chiesi manufactured inhalers (Fostair, Trimbow, Clenil brands),
2) Clip-Tone Buddy app - class I medical device accessory (CE marked), available on Apple and Google app stores.
Both parts of the system are independently protected by patents (granted and pending) - a collaboration agreement is in place clearly delineating background and foreground IP ownership.

Study design
General points:
Although the CTS is currently available (Clip-Tone on prescription and Clip-Tone Buddy app available to purchase on App store) we currently do not know how effective it is in improving and maintaining inhaler technique in patients with asthma. If this data were available, health care professionals would know whether to advise patients to use it. Potentially this is a low-cost solution to a large problem within the asthma community.

In order to gain this evidence, it is important to compare the use of the CTS with "usual care". Some patients will already have good inhaler technique and have adequate education on how to use their inhaler – we do not want to interfere with this and so all patients in the study will continue to see their HCPs as and when they are invited to do so or if the need arises during the study. We will simply ask patients to report what input they have had when we follow them up at each visit. We plan to randomly assign half the participants to the CTS, along with their "usual care" and half to continue with their "usual care" only.

During the Covid pandemic patients have become accustomed to having many of their health consultations performed remotely by video or telephone consultation. The public in general have become used to talking with friends, family, colleagues and having work meetings via Zoom, Microsoft Teams or Facetime. Virtual consultations generally are time saving with no travel time

for participants and easier to fit into our everyday lives. Participants who enter into this study need to have the availability of a mobile smartphone or a tablet in order that they can participate. For these reasons we have planned to carry out the study using virtual consultations. We appreciate that the nature of the study will exclude some members of the public but with smartphone ownership at >90% of all UK under 65-year-olds (OFCOM data 2020) the numbers excluded in this study will be small.

We will reassess recruitment within the first 4-8 weeks of the study and if it is felt participants are being excluded because they want to have face-to-face consultations rather than virtual ones, we will source rooms to see participants and submit an amendment to the protocol and ethics committee.

In developing the project plan we have collaborated with Greater Manchester Clinical Research Network (GMCRN) Study Support Services Lead, and Speciality Lead for Primary Care, Dr Sheila McCorkindale, who have contributed to the study design and advised on recruitment strategy. We have had input from patients and public through the GMCRN Research for Futures group and have enlisted a patient to be part of our trial management group to help throughout the study. We have also had advice from North West Research Design Service on study design and sample size.

Methods:
We will carry out a randomised controlled study comparing inhaler technique in those using Clip-Tone System (CTS) with standard care (the “usual care” group) over a 6 month period.
Through the GMCRN, primary care practices will be asked to search their databases and identify patients meeting the inclusion criteria. Greater Manchester covers a wide area with diverse populations, including geographical (urban and rural), socioeconomic, ethnicities and ages. Using text messaging services patients will be informed about this study and be directed to an online recruitment portal which will consist of a short questionnaire to include/exclude potential participants. This questionnaire will also include questions related to equality and diversity to allow assessment of whether the opportunity to participate is reaching a broad range of eligible patients. It will include access to the detailed patient information sheet (PIS). If the patient is identified as potentially eligible the researcher will arrange an appointment. In addition, we will advertise the study in health care settings, e.g., GP practices and pharmacies and potential recruits will be able to access the website or call the research team directly to obtain verbal study information, complete the eligibility questionnaire and receive the PIS.
We hope to have kept the inclusion criteria as broad as possible in order to reflect real world testing of the CTS as much as possible.

Eligibility Criteria:
1) Over the age of 16
2) Self-reported asthma diagnosis and currently receiving treatment
3) Must be regularly prescribed one of the following brands of inhaler – Fostair, Seretide, Flixotide, Clenil, Trimbow (those that fit the Clip-Tone E or F) and have been using it for at least 1-month prior to enrolment.
4) Access to a smartphone or tablet device and willingness to use it to regularly assess inhaler technique for the study duration.

Exclusion criteria:
1) Using a spacer to assist with using their inhaler.

2) Prescribed oral steroids for asthma in the preceding 1-month
3) Medication is not self-administered
4) Treatment for acute asthma in an ICU within the previous 3 years
5) Insufficient understanding of spoken and/or written English (as judged by the researcher).

Potential recruits will attend a baseline visit where formal content to participate will be taken and eligibility criteria checked. Initial inhaler technique will be assessed using a formal inhaler technique score. Asthma control questionnaire will be completed (a validated asthma questionnaire to detect level of asthma symptom control). Some baseline questions will be asked about their asthma e.g. medication, exacerbations, HCP involved.
We plan to randomise 126 participants, half to CTS and half to Usual care.

Those allocated to the CTS group will have the Clip-Tone posted to them along with a voucher code for the Clip-Tone Buddy App and a short virtual visit will be arranged the following week to ensure the participant knows how to use the device and the features of the app.

Participants will all attend 3 further follow-up visits in 1, 3 and 6 months. For the "usual care" group these visit dates will be calculated from the baseline appointment, and for the CTS group these will be calculated from the training visit. The difference in these calculations is to allow for any delay in the participant commencing use of the CTS, to ensure that 6 months of active intervention usage are accurately recorded.

At each follow up visit inhaler technique will be assessed using the formal inhaler technique score. Asthma control questionnaire will be completed and a few questions will be asked about asthma health care utilisation since the previous visit. Those in the CTS group will be asked to send a screen shot of the app use and to give some feedback on useability, frequency of use, barriers to use and suggested improvements.

At all study visit all patients will also have their inhaler technique video recorded. For the Baseline (V1) and the final visit (V4) these recordings will be scored blindly (not knowing which group they are in) by an independent assessor. This is to reduce the element of bias in the study, as the participant and researcher carrying out the visit will know if they are using the CTS. Participants can opt out of this should they wish. At the other two visits, at one month (V2) and three months (V3) the inhaler technique will also be recorded but only to allow for the researcher to review the technique post visit, to ensure correct assessment results. These recordings would be destroyed directly after this is completed and not sent for blind assessment.

We hope to recruit patients over a 9-12 month period from June 2021. Patients will be in the study for 6 months.
Participants will be offered a small payment for each visit they attend (£15), as a thank you and recognition of any inconvenience caused.
At the end of the study the CTS group can keep using the app should the wish and the "usual care" group can be sent one to use should they wish to try it out.

Each participant will be enrolled in the study for approximately 6-months. Participants will self-refer into the study, via short online questionnaire. They will be asked a few basic questions to check eligibility (see section: 6.3). Following initial eligibility check, a patient information sheet will be sent to the patients and contact with the patient will be made. If the patient is willing a

baseline appointment will be made. At this baseline appointment consent will be obtained. Following consent some demographic details and asthma history will be obtained and the participant will be randomised.
If they are allocated to the intervention group, a Clip-Tone device will be sent to them, along with details of the app and how to upload it and a follow up training session will be made to ensure the participant can use the CTS.
After the baseline visit all participants will be asked to attend three further follow-up visits, 1-month, 3-months and 6-months later.
At all of the visits participants will be asked to demonstrate their inhaler technique which will be observed and scored according to the inhaler technique checklist. This demonstration will also be video recorded, at baseline (V1) and final visit (V4) this is to enable a blind assessment of their technique by an independent observer and at month 1 (V2) and month 3 (V3) only for researcher assessment, prior to immediate destruction. The table below summarises the appointments and what will happen to participants during the study.

	Pre-screening (pre-consent)	Baseline Appointment: T=0	Training for intervention arm: T=7days (+/-7)	Visit 1: T=28 days (+/-7 days)	Visit 2: T=90 days (+/- 14 days)	Visit 3: T=182 days (+/- 28 days)
Database searches	X					
Participant initiated eligibility screen	X					
Informed Consent		X				
Demographics		X				
Relevant clinical history		X		x	x	x
Recorded Inhaler technique (for blinded assessment)		X				X
Recorded Inhaler technique assessment		X		X	X	X

(by researcher)						
Asthma Control Questionnaire		X		X	X	X
Randomisation		X				
Training on use of intervention			X			

5.3 End of study

A participant is considered to have completed the study if they have completed the baseline assessment, the intervention guidance appointment (if randomised to the intervention group) and the follow up appointments at 1, 3 and 6 months. As a minimum at the baseline and all follow up appointments, inhaler technique assessment and ACQs will be completed. Participants may opt out of the video recording of inhaler use if desired (these blinded assessments are intended to verify the veracity of the researcher assessment who cannot be blinded due to the nature of the intervention).

6 STUDY PARTICIPANTS

6.1 Inclusion Criteria:

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1) Provision of signed and dated informed consent
2) Willingness to comply with the study procedures and confirmed availability for the study duration.
3) Over the age of 16
4) Self-reported asthma diagnosis and currently receiving treatment
5) Must be regularly prescribed one of the following brands of inhaler and have been using it for at least 1-month prior to enrolment:
    - Fostair pMDI (100 mcg Beclometasone/ 6 mcg Formoterol per dose; 200 mcg Beclometasone/ 6mcg Formoterol per dose); Chiesi Ltd
    - Clenil Modulite pMDI (50 mcg, 100 mcg, 200mcg or 250mcg Beclometasone per dose); Chiesi Ltd
    - Trimbow pMDI (87 mcg Beclometasone, 5 mcg Formoterol, 9 mcg Glycopyrronium per dose); Chiesi Ltd

- Seretide Evohaler pMDI (50 mcg Fluticasone/ Salmeterol 25 mcg per dose; 125 mcg Fluticasone/ Salmeterol 25 mcg per dose; 250 mcg Fluticasone/ Salmeterol 25 mcg per dose); GSK UK Ltd.
- Flixotide Evohaler pMDI (50 mcg Fluticasone per dose; 125 mcg Fluticasone per dose; 250 mcg Fluticasone per dose); GSK UK Ltd.

6) Access to a smartphone or tablet device and willingness to use it to regularly assess inhaler technique for the study duration.

6.2 Exclusion Criteria:

An individual who meets any of the following criteria will be excluded from participation in this study:

1) Using a spacer to assist with using their inhaler.
2) Prescribed oral steroids for asthma in the preceding 1-month
3) Medication is not self-administered
4) Treatment for acute asthma in an ICU within the previous 3 years
5) Insufficient understanding of spoken and/ or written English (as judged by the researcher).

6.3 Recruitment

It is anticipated that 160 patients will need to volunteer to be screened for eligibility in order to reach the target enrolment size of 126.

The study will be publicised through direct mailing to volunteers already on a database kept by Research for the Future (researchforthefuture.org – an NHS backed campaign to help people find out about and take part in research) and via social media forums.

The study will be adopted on to the NIHR clinical research network (CRN) portfolio. We have already been working with the Greater Manchester CRN who have advised how recruitment can work. Via the CRN portal GP practices will be able to participate in publicising the study to their patients who may be eligible. Practices will search their database for patients with asthma who are using one of the relevant inhalers and who have consented to receive information about research studies. Text messages will be sent to these potential participants.

The message to potential participants from any of these sources will contain a link to a website which will have more detailed information about the study and a short set of questions. By answering and submitting the questions along with contact details the participants will be sent a copy of the PIS and will be consenting to be further contacted by the researcher. The researcher will then contact the potential participant and discuss the details of the study, no less than 24h and no more than 1-week following the submission. If the participant is willing an appointment will be arranged where following further discussion the participant will be asked to provide full informed consent.

Informed consent will be obtained through verbal agreement. Participants attending the baseline appointment will be asked to confirm that they have received and read the written information (PIS). If they have not received a copy this will be provided for the participant to read during the appointment. If they request additional time to consider the appointment will be rearranged. The researcher will read through a scripted summary of the study and record answers to specific consent questions. If the participant prefers (for example if they have literacy or language concerns) they will be offered a more comprehensive scripted summary. Any questions the participant has will be answered by the researcher. The researcher will record the answers to the questions and the participant's consent and sign the form in the presence of the participant. A copy of this will be sent to the participant.

These appointments will be held on a virtual platform such as Zoom.

6.4 Randomisation:

Once consent has been obtained and baseline data has been gathered, participants will then undergo simple randomisation. Approximately 50% of people will be allocated to each group. Allocation into the study group will be carried out by the dedicated researcher. Prior to the recruitment of the first patient a random sequence of 150 (greater than the number that will ultimately be recruited) will be generated using the website random.org/sequence. Each participant will be allocated the next available number of the randomly generated sequence. If this is an even number the participant will be allocated to care as usual group and if this is an odd number they will be allocated to the intervention group. For those allocated to the intervention group, a Clip-Tone device along with instructions how to download the app will be sent to them by post and a training appointment will be made. Because of the nature of the intervention, it is not possible to blind participants to which group they are allocated to.

6.5 Participants who withdraw consent [or lose capacity to consent]

Participants can withdraw consent at any time without giving a reason, as participation in the research is voluntary, without their care or legal rights being affected.

The investigator may discontinue a participant from the study for the following reasons:

- Lost-to-follow up; unable to contact subject (see Section 7, Lost to Follow-Up)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognised) that precludes further study participation. E.g. if a participant and their healthcare

professional agree to change the participant's device and that is no longer compatible with the Clip-Tone system.

Where given, the reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF).

Where withdrawal or discontinuation occurs at a timepoint before data has been fully anonymised, withdrawing participants may request that all of their data is withdrawn. Where data has been anonymised and it is not possible to withdraw a participant's data this will be communicated to the participant where this is possible.

Subjects who sign the informed consent form, and are randomised but subsequently withdraw, or are discontinued from the study, will be replaced, if the study timetable allows.

7 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 1 scheduled visits and study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to return to for a required study visit:

- The site will attempt to contact the participant, reschedule the missed visit within a week, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's study file.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

- Should a participant miss a study visit for whatever reason and be unable to reschedule within the timeframe of the visit schedule but wishes to continue in the study, this will be documented in the participant's study file and the following visit will be scheduled as per the study protocol.

8 OUTCOME MEASURES

Inhaler technique scores collected at the various time points will be assessed for intra patient differences (whether there is an improvement in an individual over the time period) and inter group differences (whether those using the intervention on average improved more than those

receiving care as usual). Understanding the impact of the intervention on inhaler technique will provide additional evidence to support the wider use of the intervention in clinical practice.

Many studies have previously linked improved inhaler technique with improved asthma control. By assessing whether there are differences in asthma control between the intervention and care as usual groups over the study duration, it may be possible to directly link the intervention with improved disease management. It is important to note that this study is not powered to determine this but exploring this may provide some preliminary data on this issue which may be investigated in the future.

If the results of the study demonstrate a positive outcome in this group of participants, this will provide a foundation to investigate the utility of the intervention in other groups, such as those who use inhalers for COPD.

9 DATA COLLECTION, SOURCE DATA AND CONFIDENTIALITY

All data collected will be directly recorded in an electronic clinical record form (eCRF) management system such as Teamscope. All data collected will have a secure audit trail with clear visibility of when, where and who made or modified entries. Data will be encrypted and stored in a cloud-based server which is compliant with GDPR. Any data exported from the eCRF for analysis will be anonymised. The system will also be used to upload the videos and screen captures that will be collected from participants. As soon as they have been uploaded into the eCRF they will be permanently deleted from the device on which it was recorded. Access to the eCRF will be password controlled and access limited to core team members only.

9.1 Archiving

Pseudo anonymised source data will be stored for 5 years post publication, after which it will be destroyed.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Analysis

Intention to treat analysis will assess between-group differences in the patient improvement (relative to baseline) in inhaler technique score and inhalation time (at 6 month follow-up). Assessment of in inhaler technique will be done for each visit (1-, 3- and 6-month follow-ups) using parametric and non-parametric tests of differences in distribution location (mean for parametric tests, median for non-parametric tests).

Similar analysis will be performed on a secondary outcome measures – asthma control score (obtained from the ACQ).

More complex analysis, e.g., mixed-effects (multi-level) models, to study the temporal evolution of the primary and secondary outcomes will only be performed if is deemed warranted by the results of the initial between-group analysis.

The proportion of patients in each group at each visit with a correct inhaler technique (achieving maximum score of 10) will be compared within groups over each visit. Comparisons will be made within groups and between groups, using appropriate tests of the follow-up specific 2x2 contingency tables.

We will seek to examine any correlation between frequency of use of the Clip-Tone system in the intervention group to mean inhaler technique scores. Identification of most frequent errors in each group will also be explored (i.e., does CTS have an impact on particular steps?).

We will also intend to carry out per-protocol analysis which will include those participants in the intervention group who used the Clip-Tone Buddy at least once per week in the first month and at least once per fortnight in thereafter. Appropriate parametric and non-parametric tests will be used.

Descriptives of frequency of CTS use and change of use over time will also be carried out. Characteristics of participants who had higher compliance will also examined to identify if the Clip-Tone Buddy app had particular suitability for particular groups of people.

10.2 Sample Size

To calculate the sample size, we identified previous studies examining interventions to improve inhaler technique. To appropriately power the study to understand if the intervention has a significant impact on improving inhaler technique, or if any improvement observed is as a result of chance (i.e., no significant difference between the intervention and care as usual groups) we will recruit 126 participants. The sample size calculation has been carried out using data from a previous study [20]. In this study, participants had a mean baseline score of 6.8 in both the intervention and control groups. At the end of the study participants in the control group had a mean score of 8.9 (s.d. 1) and the intervention group had a score of 9.5 (s.d. 1). Assuming that the intervention studied here will have a similar impact we calculate a minimum sample size of 88 will be required to power the study to a 0.05 significance level. Recruitment of 126 patients will allow the study to still be adequately powered with up to a 30% drop-out rate. The power calculation takes account of the likelihood that participants in the care as usual group will also be likely to show some improvement in technique.

11 MONITORING AND QUALITY ASSURANCE

A trial management group consisting of Prof Clare Murray (Co-Lead applicant and study Chief Investigator), Dr Elizabeth Crawford (Co-Lead applicant for the funding application and SME representative, Miss Naomi Brooke (the researcher) and Mr Antony Jankunas (patient representative) will meet 2-4 weekly to oversee the day -to day running of the study. When required the study statistician, technical support person, Prof Tariq Aslam and representative from the CRN will attend.
The study progress will be formally overseen by the Research Steering Group (RSG) who will meet quarterly. This will be chaired by Dr Helen Marsden (independent industry representative with expertise in running clinical studies) and will consist of at least one other independent member and the statistician. Prof Clare Murray (Co-Lead Applicant and study Chief Investigator) and Dr Elizabeth Crawford (Co-Lead Applicant for the funding application and SME Representative) will report to this committee. A NIHR representative will also be invited to attend. During these meetings progress of the clinical study towards milestones will be reported, any difficulties will be highlighted and agreement of plans for rectification (if required) will be agreed.
Due to the nature of the study a data monitoring committee is not felt to be required.

The study will be formally monitored and audited by the sponsor (University of Manchester).

12 SAFETY CONSIDERATIONS AND ADVERSE EVENTS

We do not anticipate any risks to the participant from using the CTS or significant adverse events.
Due to the nature of the study a data monitoring committee is not felt to be required.
Asthma exacerbations will be captured as an outcome when questions about asthma control are captured at each follow-up visit and as such will not be recorded as an adverse event.

However, all SAEs (defined as: defined as any event that results in death; is life-threatening; requires hospitalisation or prolongation of existing inpatient's hospitalisation; results in persistent or significant disability or incapacity; is a congenital abnormality or birth defect) will be recorded from the time the participant is recruited into the study until the completion of the final visit or the subject has been withdrawn. Reporting of any SAE will follow the University of Manchester standard operating procedure for Responding to Research Related Compliance Incidents (see http://documents.manchester.ac.uk/display.aspx?DocID=23493).

Briefly, all SAEs must be recorded on the SAE form and the SAE form must be sent to the Sponsor within 24h of being notified of it. Research Ethics committee will also be informed. All SAE forms will have an assessment of relatedness and expectedness. When an AE/SAE occurs, it will be the responsibility of the Chief Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information on the SAE form (if the AE meets the criteria of serious).

Listings of adverse events will be provided to the Sponsor when requested.

13 PEER REVIEW

The study has been funded through the NIHR i4i Product Development Award funding scheme.

The process included three stages including written outline application, written full application and spoken presentation in front of a multidisciplinary panel. Each written application was reviewed by four independent reviewers, three of whom were clinicians, researchers in a similar field or statisticians and the fourth was a member of the public who has experience of using inhaler devices. Following feedback and before final approval of funding, we made some suggested further amendments to the study plan which were accepted.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Approvals

The study will be conducted in in full conformance with all relevant legal requirements and the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and the UK Policy Framework for Health and Social Care Research 2017.

The study protocol will receive a favourable opinion of the Greater Manchester (GM) East REC and HRA prior to any participant recruitment.

The sponsor will ensure that the study protocol, PIS, ICF, GP letter and submitted supporting documents have been approved by a REC prior to any participant recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation. Annual Progress Reports will be submitted to the Research Ethics Committee (REC) and the Sponsor in accordance with local and national requirements. The CI and sponsor will ensure that the REC is notified that the study has finished (either as expected or prematurely) within required timeframes with summary reports to be provided as required.

14.2 Risks

The Clip-Tone System is formed of two parts which are developed by different manufacturers. The hardware part – the Clip-Tone – has two variants – Clip-Tone E (compatible with Evohaler brand of inhalers) and Clip-Tone F (compatible with Chiesi branded inhalers). These devices are regulated as class I medical devices. A full risk assessment according to ISO 14971 – medical device risk management standard – has been carried out.

Clip-Tone: Residual risks

- The Clip-Tone is not suitable for cleaning in a dishwasher. Putting the device in the dishwasher may damage the plastic moulding and lead to removal of the sound signal or alteration of the flow rate at which sound frequencies are emitted. This may lead to incorrect inhaler guidance being provided to users.
- In order for the audio signal to be generated via the Clip-Tone, it is necessary for an airflow to be generated through the inhaler and Clip-Tone. If a user covers the inlet, for example with fingers performance may be affected. This will be pointed out to the participant when use is demonstrated and will be highlighted in the written instructions provided to the participant.
- If debris is allowed to enter the inhaler device or Clip-Tone this may present a risk to a user inhaling.

Clip-Tone Buddy: Residual risks

- Background sounds may interfere with the app and provide a false view of a person's inhaler use. This should be evident to the user if it occurs, and participants will be advised to use it in a relatively quiet environment.
- The information provided in the app should not be used to make clinical decisions. Participants will be advised to use their medication as advised by their healthcare professional.

15 STATEMENT OF INDEMNITY

The University has insurance available in respect of research involving human subjects that provides cover for legal liabilities arising from its actions or those of its staff or supervised students. The University also has insurance available that provides compensation for non-negligent harm to research subjects occasioned in circumstances that are under the control of the University.

16 FUNDING and RESOURCES

Funding for the study has been provided via NIHR i4i Product Development Awards (ref: 202884).

17 PUBLICATION POLICY

Results will be presented at national and international scientific meetings. All results will be published in general medical journals using open access policies. We will communicate the results to the general public, specifically to those with asthma via our PPI groups (VOCAL). We anticipate that Asthma UK (involved in this specific i4i call) will assist with publication of results, by distribution via their website and Twitter feeds. A summary of the main study findings will be sent to all participants.

Results of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the Investigator(s) are completed.

The results may be published or presented by the Investigator(s), but the Funder will be given the opportunity to review and comment on any such results for up to 1 month before any presentations or publications. Professor Clare Murray, Dr Lizzie Crawford and Prof Tariq will need to approve authorship and publication of any manuscripts or abstracts.

A Clinical Study Report summarising the study results will be prepared and submitted to the REC and MHRA within 6 months of the end of study.

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