REG STUDY PROTOCOL

Title (long): The impact of inhaler choice on climate change and personalised healthcare

Title (short): INHALER CHOICE & ENVIRONMENT (ICE)

REG Project code (if available): REG-RES2008
Date: 26/07/2021

Research Protocol developed by Omar Usmani in collaboration with The Respiratory Effectiveness Group

CONTENTS

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1. STUDY PERSONNEL CONTACT INFORMATION

Study Chief Investigator:
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2. PROTOCOL SUMMARY

Title of Study: Inhaler Choice & Environment

Protocol version: 1.0

Study Number: REG-RES2008
Chief Investigators: Dr Omar Usmani

Clinical Research Organisation: Respiratory Effectiveness Group

Study funder: AstraZeneca, Boehringer Ingelheim, Chiesi Ltd, Kindeva

Study Sponsor: Respiratory Effectiveness Group

Name of Active Ingredients: NA

Name of Investigational Product: NA

Phase of Clinical Development: NA

Number of Investigational Centres Planned: NA

Country of the study: International, multiple

General Design and Methodology: This is a short cross-sectional study disseminating surveys to asthma/COPD patients and healthcare professionals.

Objectives: This project will explore the perceptions of asthma/COPD patients and Healthcare Professionals (HCPs) on inhaler choice and its impact on climate change and personalised healthcare. The following objectives will be achieved:

1. Identify experience and preferences of patients and healthcare professionals (HCPs) of inhaler choice / change in relation to climate change and personalised healthcare (i.e., a patient's autonomy in decision making about their own healthcare plan).
2. An extensive literature review covering current discussion on the above topics.

Number of Patients Planned: NA

Study Population: It is planned to enroll asthma/COPD patients and HCPs involved in the care of asthma / COPD patients.

Length of the Study: Study is cross-sectional. Study period will be 3 months, where each window for patient / HCP participation will be an email / post sent to participate at initial recruitment and a reminder 1 month later.

End of the Study: Surveys will be closed after 1 month after final reminder has been sent.

Inclusion Criteria: Patients may be included in the study if they meet all the following criteria:

- Clinically stable asthma or COPD diagnosis
- Prescribed inhaler medication
- Age >18 years

HCPs may be recruited if they meet the following criteria:

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- Work in the field at time of participation
- Interact with asthma/COPD patients

Exclusion Criteria: Patients will be excluded from participating in this study if they meet any of the following criteria:

- Unable to access questionnaire
- Unable to understand the electronic questionnaire process
- Using a non-MDI/DPI/SMI device

Investigational Product: NA (non-interventional study)

Placebo: NA (non-interventional study)

Blinding: NA (non-interventional study)

Method of Randomization: NA (non-interventional study)

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3. ABBREVIATIONS AND DEFINITIONS

Table 1. Abbreviations

Abbreviation	Definition
CFC	Chlorofluorocarbon
COPD	Chronic Obstructive Pulmonary Disease
DPI	Dry Powder Inhaler
GWP	Global warming potential
HCP	Healthcare professional
HFA	Hydrofluoroalkane
HFC	Hydrofluorocarbon
pDMI	Pressurised Metered Dose Inhaler
SMI	Soft Mist Inhaler

4. BACKGROUND

Medications for asthma and COPD are mostly administered using inhaler devices. Inhalers are crucial to managing daily symptoms, acute emergencies and chronic disease. Most of the current inhaler devices available provide therapy using one of three drug delivery systems: dry powder inhalers (DPI), metered-dose inhalers (MDIs +/- spacers/holding chambers, and breath-actuated MDIs) and soft mist inhalers (SMIs). DPIs are breath-activated, where the patient requires deep and forceful inhalation, whereas MDIs require patient coordination of inhalation and actuation of the inhaler, and SMIs are propellent free. Until the early 1990s, MDIs contained chlorofluorocarbon (CFC) propellants. These ozone-depleting substances[1] were phased out under the Montreal Protocol (1987)[2] in a global effort to address climate change. To ensure a seamless transition for patients that were already using MDIs, pharmaceutical companies developed CFC-free MDIs, replacing CFC with hydrofluoroalkane (HFA) propellants: HFA134a and HFA227ea. Although HFCs are not ozone-depleting, they still have a high global warming potential (GWP). As such, the UNEP Kigali Amendment to the Montreal Protocol, introduced the phase-down of HFCs as greenhouse gases[3]. The European Commission has now approved two F-gas regulations, the second one in 2015, granting an exemption for pharmaceutical use[4].

Most recently, the UK government provided a recent directive of the Environmental Audit Committee that stipulated that at least 50% of prescribed inhalers should be of low global warming potential by 2022[5]. The directive has recommended that stable patients using MDIs are switched to DPIs, due to the lower GWP of the latter[5], despite the higher proportion of patients in the UK using MDI inhalers[6]. There is a potentially significant impact on patient outcomes due to switching device[7], as well as an impact on the financial drive to innovate and develop greener or lower carbon MDIs[8].

Although there is currently limited discussion in the literature as to the contribution of inhaler choice to climate change[1,7–13], the potential benefits and drawbacks of the three inhaler delivery

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systems and their impact on patient care is well documented. Previous publications have considered accessibility of inhaler type to those with mobility issues or lack of understanding of proper inhaler use[14,15]; differences in efficacy between the delivery systems[16]; the impact on adherence of patients switching from one inhaler type to another[17–19]; and costs associated with each delivery method and switching inhaler type have been discussed[1,20–22]. The impact of switching inhaler on tailored and personalised healthcare has also been poorly defined, where the inability to tailor inhaler choice to patient preference[23,24] may have impact on patient understanding[25,26] and technique[27], and therefore patient outcomes[28,29].

There has been limited discussion and expert opinion on the impact of switching inhaler type and its impact on climate change and personalised healthcare. Additionally, there has been little discussion on short- and mid-term solutions to reduce the inhaler effect on climate change, such as avoiding landfills through increased recycling of inhalers and use of reusable inhalers[30–32]; and patient education to reduce the waste of medication through improper inhaler use, non- adherence and excessive use[33].

Public knowledge and discussion are being opened up through media coverage of this topic[34], policy change is driving and affecting the development and innovation of novel technologies[13], and the inevitable impact of climate change on exacerbation frequency in sufferers of respiratory diseases is of concern[35].

This research aims to gather patient-centric experiences/opinion on the impact of switching inhaler type on climate change and the suggestion of green alternatives to switching inhaler types; as well as measure the potential impact of switching on patients and their personalised healthcare plan. Extra focus will be given to switching inhaler type for non-medical reasons (i.e., based on policy change, rather than patient health requirements); and offer perspective on driving inhaler development for carbon reduction. It will also provide an update of the current discussion in the literature on the impact of inhaler choice.

5. STUDY OBJECTIVES

This study aims to:

Identify experience and preferences of patients and healthcare professionals (HCPs) of inhaler choice / change in relation to climate change and personalised healthcare (i.e., a patient's autonomy in decision making about their own healthcare plan).

This research will provide opinion and preferences of patients and health care workers on:
- (a) **Costs to environment**: The impact of inhaler choice and switching inhaler delivery system on climate change, as well as short-term vs long-term solutions for reduction of impact.

The research will also gather information from patients on:

- (b) *Personal impact:* The impact of inhaler choice / changing medication that has affected their personalized healthcare plan and inhaler use.

6. PARTICIPATING / RECRUITING CENTRES

Patients and HCPs will be recruited to participate across a range of countries. Countries will be selected for recruitment based on extended REG network and availability of patient/HCP organisations and respiratory societies. As the survey is online, there is no need for centres to recruit patients.

7. STUDY DESIGN

7.1. General design and study scheme

An extensive review of the available literature on pMDI, DPI, SMI, and the effects of switching inhaler type in relation to impact on environment and patient health care will be carried out. The literature review from the research proposal will be expanded to include new papers published in the last year and different perspectives. The literature will be used to aid the development of the questionnaires.

Patient questionnaire

Two questionnaires will be distributed for data collection. Questionnaires will be designed using advice provided by the literature[36–38], and will be approved by the *REG Environment, Epidemiology & Airwaves* scientific steering group before distribution. The first survey will recruit asthma / COPD patients prescribed inhaled medication recruited through professional networks and patient associations. A live link to the survey on SurveyMonkey will be included, and contacts will be asked to pass on to patient representative organisations and respiratory societies. Given the ongoing CoVID-19 situation, questionnaires will only be distributed electronically.

Health Care Professional survey

The second survey will be for health care professionals (HCPs) recruited through the extended REG network. This questionnaire will be accessible to participants on the SurveyMonkey platform. Patient questions will be on their personal experiences with their inhalers, questions for HCPs will be broader on their general experiences with patients. For example, a patient will be asked if they were included in the decision making choosing their inhaler, whereas an HCP will be asked if they try to generally include patients in choosing their inhaler. Like patients, HCPs will also be asked their personal attitudes and perspectives on climate change and green alternatives / recycling.

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Questionnaires will include Likert-scale questions for patients/HCPs to rate their agreement with a statement. The questionnaire will be designed with sets of questions categorised into sections as follows:

1. *Characteristics* – To gather general information on patient (such as demographics, diagnosis, inhaler switch and inhaler brand) and HCP (such as their region of work).
2. *Personalised healthcare / inhaler choice* – To identify satisfaction, opinion and considerations of patients and HCPs on their choices in inhalers/healthcare plan
3. *Inhaler satisfaction* - To ascertain patient confidence and satisfaction with their (new) inhaler
4. *Climate change* – To gain insight into awareness and attitudes towards inhaler impact on climate change, green inhaler alternatives and green alternatives to switching inhaler (such as recycling).

7.2. Study Population

Inclusion criteria

Eligible patients must meet all the following inclusion criteria:
1) Asthma / COPD diagnosis
2) Prescribed inhaler medication
3) Age >18 years

Eligible HCPs must meet all the following inclusion criteria:
- Work in the field at time of participation
- Interact with asthma/COPD patients

Exclusion criteria

Patients will be excluded from the trial if any of the following are:
1) Unable to access questionnaire
2) Unable to understand electronic questionnaire process

7.3. Outcomes

Primary outcomes

1) Experiences, preferences and understanding of asthma/COPD patients of their inhaler, their inhaler understanding, choice and climate change.
2) Preferences and opinion of HCPs on inhaler choice, personalised healthcare and climate change.

Secondary outcomes

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3) The results from the two questionnaires will inform a Delphi study to gather expert opinion on the same topic.

8. PATIENT/HCP MANAGEMENT DURING THE CONDUCT OF THE STUDY

Patients/HCPs will be contacted twice during the study. The first to invite them to participate in the questionnaire. One month later, a reminder will be sent to invite to participate.

9. STUDY TERMINATION AND PATIENT WITHDRAWAL

9.1. Study termination

There are no formal rules for early termination of this study.

9.2. Patient/HCP withdrawal

Patients/HCPs are indicated in the consent form that they can terminate the questionnaire at any time and their responses will be deleted.

10. ADVERSE EVENT REPORTING

N/A

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Protocol amendments and deviations

Protocol amendments

No changes from the final protocol will be initiated without prior written approval and favourable opinion of a written amendment by the Research Ethics Committee (REC), except when the change involves only logistics or administration.

11.2. Study monitoring

The REG researcher is responsible for ensuring that the study is conducted according to the study protocol and other written instructions and regulatory guidelines.

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It is the responsibility of the REG researcher to ensure that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients/HCPs before they participate in the study.

12. ETHICS

12.1. Compliance with laws and regulations

This study will be conducted in line the principles of the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) Code of Conduct and the laws and regulations of the countries in which the research is conducted.

The REG researcher is responsible for conducting the study in accordance with the procedures described in this protocol and the applicable GCP guidelines for collecting, recording, and reporting the data accurately and properly.

The chief investigator has overall responsibility for the conduct and administration of the study.

12.2. Registration of the study

The study is registered on the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) register.

12.3. Research Ethics Committees

This study has been approved by the Anonymised Data Ethics & Protocol Transparency (ADEPT) committee.

The study protocol and related forms will be submitted to an independent Research Ethics Committee (REC) in each country where ethics are required. The REG researcher is required to maintain accurate and complete records of all written correspondence sent to and received from the REC.

The study will be conducted on behalf of Dr Omar Usmani.

12.4. Informed consent

Informed consent will be obtained from each patient/HCP at the start of the questionnaire. The purpose of the study is briefly described. Participants are informed that participation is voluntary and entirely anonymous. Patients consent to their data being used by clicking the 'agree' to participate button which confirms they have read the information on the consent form, that they voluntarily agree to participate and that they are over 18 years. When clicking the 'agree' button they begin the

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questionnaire. When clicking the 'disagree' button they are taken to a disqualification page with further information on REG.

12.5. Confidentiality regarding study patients/HCPs

The REG researcher will assure that the privacy of the patients/HCPs, including their identity and all information is maintained at all times. Questionnaire answers will be sent to a link at SurveyMonkey.com where data will be stored in a password protected electronic format. Survey Monkey does not collect identifying information such as name, email address, or IP address. Therefore, responses will remain anonymous.

13. STATISTICAL ANALYSIS

Analyses of survey results
Descriptive statistics will be used to identify the strength of opinion/knowledge of healthcare workers and patients. Subgroup analysis will be used, as appropriate, between healthcare worker types and differences in patient age, time since inhaler switch, demographic, and whether the patient is diagnosed with asthma or COPD. Statistical analyses will follow standardised parametric tests within and between responses. Furthermore, correlations between patient and HCP responses will be calculated where appropriate.
All tests will be two-tailed, and significance set at 0.05. Analysis will be performed using R software (https://www.r-project.org).

13.3. Missing data

The per-protocol will not account for missing data as missing data will be seen as a protocol violation and therefore a patient with missing data will be excluded from this population.

14. REPORTING AND PUBLICATION OF RESULTS

Results of this study will be presented at at least one international respiratory congress (e.g. the European Respiratory Society, American Thoracic Society or similar).

These results will inform the survey design for a follow-up Delphi study. The results of this study will be written up and compared to the literature, leading to the development of a manuscript for submission to a peer-reviewed journal.

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The chief investigator and REG researcher will be authors on the manuscript provided they meet the ICMJE authorship guidelines - http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html

15. TIME SCHEDULE AND DELIVERY

The total length of the study will be approximately 7 months for the patient / HCP questionnaires.
Table 1. Anticipated study timelines

Study element	Time frame	Milestone/Delivery Date
Finalisation of protocol, centres and ethics/ approvals	1 month	Aug 2021
Commence patient recruitment		Aug 2021
Complete patient recruitment	N/A	Oct 2021
Complete data collection	2 months	Oct 2021
First baseline manuscript	2 months	Dec 2021
Publication	2 months	Feb 2022

16. FUNDING

This study will be sponsored by the Respiratory Effectiveness Group with funding from AstraZeneca, Boehringer Ingelheim, Chiesi Ltd and Kindeva.

17. PROPOSED RESPONSIBILITIES

REG run this study, which will be led by the chief investigator, Omar Usmani, from the National Heart and Lung Institute (NHLI), Imperial College London & Royal Brompton Hospital in London. The REG researcher will be responsible for data collection, management and analysis, and write-up for the manuscript.

Table 2. Study phase durations

Study phase	Time required

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Project management	52 days
Protocol development	5 days
Study set up, ethics & regulatory affairs	7 days
Patient recruitment	3 days
Data collection	2 days
Data management	40 days
Data analysis	20 days
Conference presentation	7 days
Manuscript writing & submission	27 days
Total	**163 days**

18. STEERING COMMITTEE

The study will be overseen and implemented by an independent, international steering committee. The steering committee will aid questionnaire development and review the final study report and interpret the findings in terms of their clinical importance. The committee will also oversee and co-author the final study manuscript(s).

The members of the committee include:

Omar Usmani, National Heart and Lung Institute (NHLI), Imperial College London & Royal Brompton Hospital (RBH), London, UK

Sinthia Bosnic-Anticevich, Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia

Nicolas Roche, Paris Descartes University, Cochin-Broca-Hôtel-Dieu Hospital Group, Paris, France

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