SAQ
Severe Asthma Questionnaire (Quality of Life)

Body Reprogramming as an adjunct to biologic administration in patients with Severe Asthma: a feasibility study

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Sponsor

Royal Devon and Exeter NHS Foundation Trust is the research sponsor for this study. For further information regarding the sponsorship conditions, please contact the research sponsor at:

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Funder

GlaxoSmithKline

This protocol describes a study to assess the feasibility of adapting and using a novel intervention, Body Reprogramming, for patients with severe asthma. It provides information about procedures for entering participants into the study. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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Glossary of Abbreviations

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trials
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC/SPC	Summary of Products Characteristics
SOP	Standard Operating Procedure
TMF	Trial Master File
TSG	Trials Steering Group
SAQ	Severe Asthma Questionnaire
ACQ	Asthma Control Test
GINA	Global Initiative for Asthma
GRCQ	Global Rating of Change Questionnaire

Keywords

Severe Asthma

Biologic treatment

Body Reprogramming

Study Summary

Title	Body Reprogramming as an adjunct to biologic administration in patients with symptomatic Severe Asthma: a feasibility study
Design	A feasibility study of Body Reprogramming (BR) in 2 patient groups one as an addition to normal treatment and one provided before starting a biologic treatment
Aims	• To assess the feasibility and acceptability of BR to people with severe asthma, • Using patient and other feedback to adapt and optimise the intervention for people with severe asthma.

Outcome Measures	• Number and percentage of participants taking part and completing the course including those completing the following questionnaires
	  o Severe Asthma Questionnaire (SAQ)
	  o General Symptom Questionnaire (GSQ) or GSQ-Asthma (GSA-A)
	  o Positive and Negative Affect Schedule (PANAS)
	  o Asthma Control Questionnaire (ACQ)
	  o Global Rating of Change questionnaire (GCRQ)
	• Attendance to Body Reprogramming Zoom calls
	• Feedback received using the Friends and Family Test (FFT)
	
	Qualitative data from the focus groups or interviews analysed using thematic analysis concerning participants' experiences of Body Reprogramming.

Population	Patients with symptomatic severe asthma attending the regional severe asthma clinic in RD&E Hospital Devon.
Eligibility	**Phase 1** Patient has severe asthma as per ERS/ATS definition and is receiving high dose inhaled corticosteroids as defined by NICE (Appendix 2) AND Eight or more non-respiratory symptoms per week recorded on the GSQ **Phase 2** Patients with severe asthma who have been approved to commence a biologic treatment for their severe asthma
Duration	15 months
Timelines	See Gantt Chart (Appendix 1)

1. INTRODUCTION

1.1 Background

Research and clinical experience show that severe asthma is a polysymptomatic disease and that the contributions to health related quality of life (HRQoL) disutility is complex (1). As such, patients often live with a number of symptoms (related to both the disease and treatment) and including a high level of extra-pulmonary symptoms, all of which actively contribute to HRQoL deficit (2).

Our research demonstrates that the HRQoL deficit in patients with severe asthma is affected by both pulmonary and extra-pulmonary symptoms (e.g. mental fog, fatigue, unexplained pain) that contribute equally to the total HRQoL deficit (3). We have also shown that the frequency and severity of extra-pulmonary symptoms in severe asthma are similar to those in patients diagnosed with syndromes of medical unexplained symptoms such as fibromyalgia and chronic fatigue syndrome (4), two conditions where outcome is improved by lifestyle change. The current Covid-19 pandemic places additional lifestyle burden on patients with severe asthma as these patients fall into the high risk category.

1.2 Rationale for Current Study

When assessing the impact of management and treatment interventions aimed at improving HRQoL, it is important to look beyond the lung. In a cross-sectional study of severe asthma, we found that the frequency of extra-pulmonary symptoms significantly increased with the cumulative burden of systemic corticosteroids. However, those patients on biologic treatments had lower symptom scores irrespective of their systemic steroid burden (4).

We hypothesize that a specific intervention aiming to optimising patient knowledge on disease management, physical activity, relaxation (5) and other psychological and biological lifestyle changes that increase well-being and mood, may lead to improved self-management. Severe asthma patients lack any form of rehabilitation provision analogous to pulmonary rehabilitation, which is an evidenced-based education and exercise programme for people with COPD and has additional benefits on top of drug therapies (6). Indeed evidence shows that pulmonary rehabilitation should be provided prior to stepping up drug treatments in COPD , leading to the hypothesis that a similar provision for severe asthma patients prior to

starting new treatments such as biologics would enhance response to treatment. Furthermore there is emerging evidence that pre-habilitation improves outcomes in high risk patients undergoing surgery and is now being recommended to improve resilience in the face of the SARS-Cov-2 pandemic (7). BR may well act as a strategy to promote resilience to Coronavirus amongst an at risk group of severe asthma patients.

We hope to see greater HRQoL improvements from severe asthma patients who have been "primed" by an education and behaviour change programme when they start biologics. Biologic therapies have a highly specific mode of action and may therefore interact positively with any reduction in systemic inflammation resulting from lifestyle improvement. We have provided a detailed theoretical rationale for potential mechanisms (8).

1.3 Patient and Public involvement (PPI)

The original Body Reprogramming course structure and narrative was developed for and with patients with fibromyalgia (9). People with fibromyalgia have a wide variety of symptoms many of them shared with people who have severe asthma (4). The present study is to examine the feasibility of an adaptation of the original course, an adaption specifically designed for people with severe asthma.

The adapted course content consists of four half hour sessions designed to be presented via Zoom video call. The content of the course (Appendix 6) was discussed with a group of 8 severe asthma patients and edited based on patient feedback. While most of the patients were happy to take part in an intervention run in groups, some interpreted the group nature of Body reprogramming as a form of "group therapy" where problems were discussed amongst the attendees. The wording of the patient information leaflet and course information was amended to clarify that Body Reprogramming is considered an educational intervention where participants attend a series of presentations. It is now worded to make clear that patients can choose whether or not they say anything during the presentations. They have the opportunity to ask questions but there is no requirement for active participation.

Originally, Body Reprogramming was delivered in person over 7 weeks at a patients treating hospital. However, in response to the UK national Covid 19 regulations and social distancing rules, this study will be delivered via the Zoom video call platform. The original 7-week course

was discussed with asthma patients who suggested that a shorter 4-week course would be more appropriate for an online intervention and that each course should last no longer than about 30 minutes.

2. Summary of Body Reprogramming

Body Reprogramming (BR) is a non-drug, multi-component intervention originally developed in Plymouth for fibromyalgia patients (see www.bodyreprogramming.org) and provided to patients through the NHS with direct referral from a GP in Devon and Cornwall. BR is applicable to any patients whose polysymptomatic presentation cannot be explained by current disease models (10). The aim of BR is to improve general health and well-being by evidence-based lifestyle change. The unique feature of BR is a theoretical model that personalises lifestyle advice to the particular patient and provides patients with a narrative that explains how and why the changes can produce benefit.

The theoretical model proposes that symptoms result from a network of biological symptom causing mechanisms (11). The extra-pulmonary symptoms of severe asthma can be explained by inflammatory mediators being part of this network that include, but are not limited to, non-specific pro-inflammatory cytokines (8). Patients are provided with a simplified version of the theory based on an analogy of ‘hardware’ and ‘software’ faults in a computer (9).

3. Study Design

This is an unblended observational study, single-site feasibility study in two phases:
<u>Phase 1 Proof of concept.</u>

The aim of this study is to assess the feasibility and acceptability of BR, whilst optimising the intervention for people with severe asthma.

<u>Phase 2 Biologic priming feasibility study.</u>

Patients expected to start a biologic treatment for their severe asthma will be invited to take part in a BR course.

Participating sites include:

- Royal Devon and Exeter Hospital NHS Foundation Trust, Exeter, UK (RD&E)

4.0 Phase 1: Proof of Concept, Four-Week Trial of BR and Post-Trial Focus Groups or Interviews

4.1 Study Aims

- To assess the feasibility and acceptability of BR to people with severe asthma in a feasibility study with remote delivery via on-line groups.
- To adapt and optimise the intervention for people with severe asthma.

4.2 Primary objectives

Four-week trial of BR

- To assess patients' willingness to attend BR and engage with the intervention as measured by course attendance and by their written feedback.
- To record the user experience when participating in the trial.
- To assess patient's willingness to complete a series of questionnaires
- To get patient feedback on the appropriateness of the questionnaires for assessing improvement in larger future studies

Post-trial focus groups or interviews

- To gain qualitative feedback on patients experience of BR following their participation in the four-week trial.
- To assess the acceptability of BR for people with severe asthma.
- To understand the barriers to attending BR by speaking those who did not attend the course.

- Using all the data from participants we will adapt the BR programme before commencing phase two.

4.3 Inclusion criteria

- Aged ≥18 years attending the regional specialist severe asthma service in Royal Devon and Exeter hospitals.
- Diagnosed with severe asthma as per ERS/ATS definition.
    - Requiring high dose inhaled corticosteroids (NICE definition of high dose ICS, Appendix 2).
- Eight or more non-respiratory symptoms per week (approximately 60% of patients with severe asthma have a moderate or high extra-pulmonary symptom burden) as measured by the General Symptom Questionnaire (12).

4.4 Exclusion criteria

- Unable or unwilling to partake.
- In the opinion of the patient's treating physician, the patient has another condition which is significantly impairs their ability to take part in the BR.
- No access to the internet or appropriate IT equipment

4.5 Recruitment and consent

Patients attending a regional severe asthma service who have undertaken a systematic multidisciplinary assessment will be identified as eligible to participate by a health professional familiar with them. This multidisciplinary review is part of normal clinic practice for the identification and treatment of severe asthma patients.

By post - Patients identified as eligible to participate will be sent a Letter of Invitation (Appendix 3) by their clinician. The letter will also include a study Participant Information Leaflet and Consent Form (Appendix 4), a General Symptom Questionnaire (GSQ) and a prepaid return envelope to be used to return the completed consent form and GSQ to the patient's clinician at RD&E (study information pack). The Patient Information Leaflet includes the phone number details for the research team. The information leaflet will inform patients that they are welcome to contact the researcher if they have any questions about the

research that may be preventing from agreeing to participate. Participants will have all of their questions answered before they sign a consent form.
Patients will be asked to return a completed Consent Forms within two weeks.
The information leaflet explains that the GSQ that the patient completes will be used as an additional screening tool to assess the number of non-respiratory symptoms they experience each week.

In clinic – Alternatively, eligible patients will be able to consent to take part in the study during a clinic appointment. When possible, patients identified as eligible to participate will be contacted by a health professional two weeks before they are due to have an asthma clinic appointment (remote or face to face) and invited to participate. This contact will be made by posting a Patient Invitation Letter (Appendix 3) and Patient Information Leaflet including a consent form (Appendix 4) out to the patient. The Invitation Letter and Patient Information Leaflet will include instructions to read the material carefully and to bring the consent form with them to their next scheduled clinic appointment. Contact details for the PI, and researcher will be included on the Patient Information Leaflet and can be contacted in the case that the patient has questions.

If it is not possible to contact patients prior to the clinic appointment, they will be informed about the study during their remote or face to face appointment. At the consultation, patients who have been identified as eligible will be invited to participate. If they accept, a health professional will introduce the patient to a researcher who provides the patient with information on the study and a Participant Information Leaflet. The patient will have the opportunity to take this leaflet away with them and to think about participating before signing a consent form. A completed consent form can then be returned using a FREEPOST envelope if the patients decides to participate. Alternatively, the patient will be able to complete the consent form before leaving clinic.

Once a patient has provided a completed consent form, they will be given be given a GSQ to complete.

The Patient Information Leaflet will outline what would be expected of the patient if they chose to participate including an outline of what the Body Reprogramming course involves and how

those who participated will be invited to a focus group at the end. During the project a video of the impact of severe asthma on patients and how this may be addressed by BR will be developed and will be available as an additional online information resource to patients and their families. The Patient Information Leaflet will also contain a contact number for a member of the research team if they have any questions. If a patient wants to participate, they will be asked to provide written informed consent which includes agreement to take part in the four-week trial of BR and the post-trial focus groups or one to one interview.

4.6 Data collection Methods

Four-week trial of BR.

The intervention

Body Reprogramming will be delivered to two groups of patients. The maximum group size will be 8 patients to allow time for questions from participants. The intervention will be delivered via the Zoom video call platform. There will be four sessions and each session will consist of a 25-30 minute presentation. At the end of the presentation there will be an opportunity for patients to ask questions or raise points of interest. Each session will include a 'practice and report back next week' instruction. Participants will be provided with a list of web resources for tai chi, guided imagery, yoga and the Alexander technique (Appendix 5) and information on the course (Appendix 6). See Appendix 4 for further course details.

4.7 Data collection time points

Participants will be asked to complete a series of questionnaires (see section 4.8) when they attend the Body Reprogramming course during the first and last week. These will be posted to the participant's home address by a research nurse, completed, and returned to the patients' clinic using a FREEPOST envelope.

At the end of the course, participants will be asked to complete a course feedback form.

If participants have not returned the questionnaire within two weeks the questionnaire pack will be sent out again. If a further two weeks pass without the return of questionnaires a researcher will contact participant by phone and ask if they need assistance.

Patients will be asked to text or email the course co-ordinator if they are unable to attend a course date for any reason. Experience shows that heath and other problems can prevent patients from attending, so attendance monitoring requires this form of data.

Demographic data
The following demographic and clinical information will be collected from the participants' clinical records at baseline by a researcher:

Patient demographics:

- Age
- Sex
- Ethnicity
- Smoking status

Clinical data
Most recent spirometry (in the last 6 months),
Major co-morbidities (respiratory and non-respiratory as identified by the patient's clinician)

- Current Drug treatment
- Asthma exacerbations requiring systemic steroids in the last 12 months,
- Cumulative steroid burden in the last 12 months,
- Healthcare utilisation: hospital admissions / Emergency Department attendances in the last 12 months.

4.8 Questionnaires

Severe Asthma Questionnaire (SAQ) (Appendix 7)
The new questionnaire will provide a combined assessment of disease and its treatment on the quality of life of patients with severe asthma (13). The scale is based on existing HRQoL

scales but modified for the severe population and provides separate assessments of the effect of asthma symptoms and the effect of asthma medicines. The questionnaire has 16 items assessing experience over the last two weeks and was produced from detailed qualitative research. An additional 3 items are included to assess overall QoL during the last two weeks, and QoL during different months of the year

General Symptom Questionnaire (GSQ) (Appendix 8)
The GSQ is a 65 item questionnaire that was designed to measure the symptoms of patients with fibromyalgia, irritable bowel syndrome and chronic fatigue syndrome (12). The questionnaire assesses the frequency of extra-pulmonary symptoms, such as somatic and psychological symptoms, on a 6 point Likert scale (the value scoring for each response shown in brackets): “Never or almost never” (1), “Less than 3 or 4 times per year” (2), “Every month or so” (3), “Every week or so” (4), “More than once per week” (5) or “Every day” (6). This questionnaire was used to measure the number and frequency of extra-pulmonary symptoms reported by patients. The scale measures frequency of symptoms. This questionnaire be completed by potential participants at baseline to identify those that report 8 or more non-respiratory symptoms per week and are eligible to participate. At subsequent time points, participants will complete the GSQ-A.

General Symptom Questionnaire-A (Appendix 9)
This is an abridged GSQ consisting of 16 non-respiratory symptoms that are associated with asthma severity. It uses the same 6 point Likert scale as the full GSQ.

The Positive and Negative Affect Schedule (PANAS) (Appendix 10)
This questionnaire measures positive and negative affect and consists 20 questions in total, 10 measuring positive affect and 10 measuring negative affect. Participants respond to each question by using a 5 point scale where 1 indicates “not at all” and 5 indicates “very much”.

Asthma Control Questionnaire (Asthma Control Questionnaire) (Appendix 11)
This questionnaire contains 7 items and takes into consideration FEV1% predicted and daily use of rescue bronchodilator. Patients respond to 7 items concerning their symptom severity on a 0-6 scale (0 = no impairment, 6 = maximum impairment) (14). The questionnaire asks patients to assess their symptoms over the last week.

Note: the included questionnaires are available and validated in the majority of European languages and many non-European ones. However, if a participant requires a translation of a questionnaire that is not available, they will not be asked to complete the particular questionnaire.

Post course questionnaires

Global Rating of Change Questionnaire – Phase one (Appendix 12)
This scale will be used by participants to indicate how much better they feel since commencing a BR. The 11-point scale ranges from -5 (a great deal worse) to 5 (A great deal better) (15). The time scale is between before the start of treatment and the current assessment.
All questionnaires are presented in paper and pencil format, to be self-completed by the patient but with support if needed.

Friends and Family Test (FFT) (Appendix 13)
This is a one question questionnaire used throughout the NHS to assess patient's thoughts on a health service they regularly use. The question we will use in the FFT asks "We would like you to think about your recent experience of our Body Reprogramming. How likely are you to recommend Body Reprogramming to friends and family if they needed a similar service?
" Participants will respond on a 5 point scale from "Extremely Unlikely" to "Extremely Likely".

Questionnaire completion

Data on the number and percentage of questionnaires collected at the two time points will recorded. This data will inform participants' willingness to complete the above questionnaires.

Post-trial focus groups or interview

Focus groups will consist of 3-6 participants and moderated by one of the members of the research team with qualitative research experience (LC, MH, JL). Two focus groups will be

conducted in total, and will explore the experience of participants after participating in a four-week trial of BR.

Each focus group will last for at most 2 hours, be recorded and transcribed verbatim. The focus groups will be conducted in a non-clinical setting near to the recruiting site (RD&E) or remotely via Zoom. Participants will have their transport costs reimbursed and provided with refreshments during the discussion. They will not be paid for taking part.

If a participant declines to take part in a focus group, they will be given the option to participate in a one to one interview. Some people find group interactions challenging and the interview option will be included to make sure we do not miss out on participant feedback when possible.

Overall the direction of conversation during the focus groups or interviews will be led by the participants in order to investigate their experiences of BR. Any problems that are brought to the attention of the research team during the trial will be discussed during these conversations.

4.9 Description of Data analyses

For quantitative data

This is a feasibility study and so not powered for statistical testing. This section describes the data to be collected which will inform the design of future studies.

- The number and percentage of participants that are invited, attended and completed the BR course will be reported.
- All outcome measures will be summarised using means and standard deviations or median (range, IQR) for continuous outcomes (as appropriate), and frequencies and proportions for categorical outcomes.
- The mean difference in all recorded scores (pre and post-trial at listed time points post-trial) will be estimated and in addition using an analysis of covariance of the baseline value of the score as well as disease severity as a covariate in the model.
- The number and percentage with complete data will be reported. The missing value guidance provided for questionnaires will be used. If no guidance is provided values

will be imputed for an individual if 20% or fewer items are missing. If greater than 20% of items are missing in the questionnaire then the questionnaire score will be treated as missing and excluded from the analysis.

- The number of adverse events (AE) and serious adverse events (SAE) will be tabulated also by the number of patients reporting an event. No dictionary for coding adverse events will be used. Events will be recoded using terms of the clinical investigators choosing.
- A full statistical analysis plan will be drawn up and agreed by the CI and study team prior to the final data extraction.

For qualitative data

Once transcribed, the audio recordings from the focus groups or one to one interviews will be analysed for recurring themes. The information gained from this phase will be used to make changes to practical aspects of the BR course, e.g. length of meetings or number of weeks, as well as adapt the narrative of the course for patients with severe asthma if required.

4.10 The Number of Participants

- 12-14 participants will be recruited for this phase of the study. No formal power calculation has been performed as this is a feasibility study.

Post-trial focus groups or interviews:

All participants in the four-week trial of BR will be asked to participate in one of the post-trial focus groups or an interview. With a trial withdrawal rate of 10%, this will mean at least 10 participants complete the trial and are eligible for the focus groups. A minimum number of participants for each focus groups is 3 and we estimate that 3-4 focus groups will be needed.

5.0 Phase 2: Biologic priming study

5.1 Study Aims

- To assess the feasibility of running a remote BR course before patients commence a biologic treatment for their severe asthma.
- To assess the acceptability of BR, testing a modified intervention having learned lessons from this feasibility study, testing the performance of outcome measures to inform a potential randomised controlled trial of the intervention.

5.2 Primary objectives

- To identify patients due to commence a biologic treatment for their severe asthma in normal care and offer them the opportunity to undertake the BR programme.
- To run a BR course with these patients and assess process outcomes, quantitative and qualitative measures of the impact of the course.
- To develop an information booklet on the principals of BR for patients with Severe Asthma who are starting or have started a biologic.

5.3 Inclusion criteria

- Diagnosed with severe asthma as per ERS/ATS definition.
    - Requiring high dose inhaled corticosteroids (NICE definition of high dose ICS, Appendix 2).
- Patients with severe asthma who have been approved for biologic treatment according to national guidance and have been assessed by a multi-disciplinary team will be offered the intervention pending starting their biologic treatment.
- Patients with eight or more non-respiratory symptoms per week as measured by the GSQ.

5.4 Exclusion criteria

- Unable or unwilling to take part.
- Participated in phase 1 of the study
- In the opinion of the patient's treating physician, the patient has another condition which is significantly impairs their ability to take part in BR.

5.5 Recruitment and consent

Before commencing a biologic treatment for severe asthma in normal clinical care, patients are reviewed by a Multi-Disciplinary Team (MDT) responsible for their care. The PI at the participating hospital will identify patients eligible to take part in this study at this time. Recruitment of eligible patients will then proceed as outlined in phase one. Participants will be sent a Patient Invitation Letter (Appendix 14) and Patient Information Leaflet (Appendix 15) that describe phase two of the study.

5.6 Data collection Method

Questionnaire collection time points are the same as for phase one:

- The first and last week.

Demographic and clinical information will be the same as for phase one.
The outcome measures will be the same as for phase one.

The Global Rating of Change Questionnaire (GRCQ) (Appendix 16)
In this phase of the study the GRCQ will be used by participants to indicate how much better they feel since commencing a BR **and a biologic treatment**. The 11-point scale ranges from -5 (a great deal worse) to 5 (A great deal better) [17].

5.7 Description of Statistical Methods

The statistical methods will be the same as that for phase one. The researchers will examine whether there is any trends indicating differences in outcome between phase one and phase two

5.8 The Number of Participants

- 12-14 participants will be recruited for this phase of the study. No formal power calculation has been performed as this is a feasibility study. Two groups of BR will be run.

5.9 The Level of Statistical Significance

Not applicable

5.10 Withdrawal criteria for both phase one and phase two

Whilst participating in the study, a patient's health or diagnosis may change. If this occurs during the study, the participant eligibility for the study they are in will be re-assessed by the clinician responsible for their care. If the participant no longer meets the eligibility criteria, their data will be removed from the database. The patient will be thanked for their time and told not to expect to be asked to participate further.

6.0 ETHICAL AND REGULATORY CONSIDERATIONS / ROLE OF SPONSOR

The study sponsor is Royal Devon and Exeter Hospitals Trust (RD&E). The various roles of the Sponsor are stated below.

6.1 Assessment and management of risk

We acknowledge the need to protect the dignity, rights, safety and wellbeing of participants taking part in this research study. Although the potential for harming participants as a direct result of being involved in the study are considered to be minimal, a contingency will be put in place, should a patient become distressed whilst taking part in the study. To begin patients will be made aware that the researchers are not there as clinicians, but as researchers. Should any patient appear distressed as a result of participating in BR or the focus groups, they will be given the opportunity to speak with a clinician. Should they have concerns about the conduct of the study, they will be given the contact details for the study CI and contact details for the Sponsor (RD&E), which will appear on the Patient Invitation Letter.

6.2 Research Ethics Committee (REC) and other Regulatory review & reports

This study is sponsored by Royal Devon and Exeter Hospitals R&D department. Positive approval from the sponsor will be obtained before submission to REC/HRA. The CI will obtain a positive opinion from a Health Research Authority (HRA) Research Ethics Committee (REC) for the study.

The CI will also require a HRA approval letter and a Capability and Capacity e-mail statement from the local R&D office before recruitment of participant's into the study.
Any amendments to the study protocol will require review by HRA (and possibly the REC if the amendment is deemed to be substantial by the study Sponsor) and will not be implemented until the HRA grants a favourable opinion for the amendment, which will also need to be reviewed and accepted by the participating NHS organisation's R&D department before they can be implemented in practice.
All correspondence with the HRA will be retained in the Trial Master File/Investigator Site File.
An annual progress report (APR) will be submitted to the HRA within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the CI's responsibility to produce the annual reports as required. The CI will also notify the HRA and Sponsor of the end of the study. If the study is ended prematurely, the CI will notify the REC, including the reasons for the premature termination.
Within one year after the end of the study, the CI will submit a final report with the results, including any publications/abstracts, to the HRA. The investigators will ensure that this study is conducted in full conformity with relevant national regulations and with the UK Policy Framework for Health and Social Care Research (2017). The research team will also bear in mind the principles of the Declaration of Helsinki when conducting the study.

6.3 Regulatory Review & Compliance

The study may be subject to monitoring by RD&E under its remit as Sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research (2017). It's current policy that the R&D Office will monitor all studies sponsored by the RD&E NHS Trust 30 days after approval of the study (from the date of Trust Capacity & Capability e-mail).
The research team will check completed study data collection documents for missing data or obvious errors.

6.4 Protocol compliance

Any additional analysis or deviations will be reported as such to the study management group and the independent study steering committee and other appropriate authorities as per Good Clinical Practice (GCP).

6.5 Data protection and patient confidentiality

In accordance with the Data Protection Act (2018), RD&E Research Data Policy, all researchers will ensure that study participants' anonymity is maintained and data is stored securely. Study participants will be assigned a study ID number which will replace the patient's name on all data. All data will be password protected, stored securely and will only be accessible by researchers and authorised personnel from UoP and RD&E. The co-investigator (Prof Michael Hyland) is employed by the University of St Mark and St John. However, as RD&E is the lead organisation, Prof Hyland will follow their data protection policy.

Following completion of data analysis, the Sponsor will be responsible for archiving the study data and essential documentation in a secure location for a minimum period of 10 years after the end of the study. No study-related records should be destroyed unless or until the Sponsor gives authorisation to do so. Medical case notes containing source data or other trial-related information should be identified by a label "Keep until dd/mm/yyyy" where the date given is 10 years after the last participant's final study visit.

6.6 Indemnity

This is a Royal Devon and Exeter Hospitals Trust (RD&E) sponsored research study. If an individual suffers negligent harm as a result of participating in the study, RD&E indemnity covers RD&E staff and those people responsible for conducting the study.

The University of Plymouth provides insurance for all of its employees through Zurich insurance. Public liability insurance is also provided by the same company. This indemnity policy can be found in Appendix 17.

6.7 Access to the final study dataset

The study incorporates the following types of data, which will only be accessed by the research team:

Qualitative data: Audio-recording of focus groups, Anonymised transcripts of focus group discussions

Routinely recorded clinic data and research questionnaires

Service use in the last 12 months;

Recruitment data (proportions of uptake, completion and attrition).
A document linking research IDs with clinical identification numbers will be created and stored in a locked filing cabinet in Bowmoor House on the site of Royal Devon and Exeter Hospital.
Anonymised data will be analysed by the research team (RJ, JL, MM, LC, and MH).
After the end of the study, anonymised information collected during the study will be made available to other researchers under an appropriate data sharing agreement, but it will not be possible to identify participants personally from any information shared.

7.0 References

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Appendix 1: Gantt chart

Timeline Post Funding	Month			Funding Confirmed	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Discuss Protocol Draft with collaborators																				
Finalise Protocol																				
Adapt patient invitation letter and information sheet for local centre use																				
Apply for Local R&D approval																				
Apply for REC																				
HRA approval																				
Brief centres																				
Identify/Recruit participants for phase 1																				
Run Phase 1 BR groups																				
Collect data from phase 1																				
Identify/Recruit participants for phase 2																				
Run Phase 2 BR groups																				
Collect data from phase 2																				
Write up																				

Appendix 2: NICE definition of high dose Inhaled Corticosteroids

Table 1 ICS dosages for adults aged 17 years and over

	Low dose	Moderate dose	High dose
Beclometasone dipropionate[1]			
Standard particle CFC-free inhalers	200–500 micrograms per day in 2 divided doses	600–1,000 micrograms per day in 2 divided doses	1,200–2,000 micrograms per day in 2 divided doses
Extra-fine particle CFC-free inhalers[2]	100–200 micrograms per day in 2 divided doses	300–400 micrograms per day in 2 divided doses	500–800 micrograms per day in 2 divided doses
Budesonide			
Dry powder inhalers	200–400 micrograms per day as a single dose or in 2 divided doses	600–800 micrograms per day as a single dose or in 2 divided doses	1,000–1,600 micrograms per day in 2 divided doses
Ciclesonide			
Metered dose inhaler	80–160 micrograms per day as a single dose	240–320 micrograms per day as a single dose or in 2 divided doses	400–640 micrograms per day in 2 divided doses
Fluticasone propionate			
Metered dose and dry powder inhalers[3]	100–250 micrograms per day in 2 divided doses	300–500 micrograms per day in 2 divided doses	600–1,000 micrograms per day in 2 divided doses
Fluticasone furoate[4]			
Dry powder inhaler	–	100 micrograms as a single daily dose	200 micrograms as a single daily dose
Mometasone furoate			
Dry powder inhaler	200 micrograms per day as a single dose a day	400 micrograms per day in 2 divided doses	Up to 800 micrograms per day in 2 divided doses