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Inhaled steroid as emergency treatment for patients with steroid dependency

Submission date
15/04/2025

Recruitment status
Recruiting

Registration date
20/06/2025

Overall study status
Ongoing

Last Edited
20/06/2025

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Patients living with adrenal insufficiency have to take daily steroid replacement medications for survival. In healthy people any stress on the body leads to an increase in the production of the steroid stress hormone cortisol by the adrenal glands. However, in patients with adrenal insufficiency, this 'reflex' release of cortisol is missing, which can lead to a life-threatening mismatch in the body's requirement for cortisol, known as adrenal crisis. The standard treatment for adrenal crisis is an emergency steroid injection; however, these injections are not always administered in time, leading to death or prolonged hospitalisation. For many patients there is reluctance or logistical delay, or the patient is too young or inexperienced to take agency for their own health with an injection that is a significant step out of their 'comfort zone'.
One way around this problem could be to use an alternative route to administer the emergency dose of steroids. It is already known that steroid inhalers, which are used all the time for asthma treatment, may administer enough steroid through the mouth and lungs to have an effect on the rest of the body, so this might be a good approach. This project will entail three small studies (with 30 ambulant patients in total) that will aim to operationalise inhaled steroids as a 'rescue' treatment to prevent or treat adrenal crisis in patients with steroid insufficiency, so this could be used in everyday NHS practice. Ultimately, this could mean that a patient with adrenal insufficiency carries an inhaler in their handbag/pocket for emergency use rather than a needle, syringe and a glass vial of steroid medication. Treating adrenal crisis earlier would inevitably reduce hospitalisations, save lives and also remove a large psychological burden from patients with adrenal insufficiency, many of whom fear that they might become suddenly ill with adrenal crisis.

Who can participate?
Patients aged over 18 years with primary adrenal insufficiency (owing to Addison's disease or bilateral adrenalectomy)

What does the study involve?
For parts A and B of the study, the participant will omit their steroid dose(s) the afternoon before attending for the study. This will be done in close contact with the study doctor, who will call the participant to make sure they are feeling good before confirming it is OK to miss the dose(s) for the study. Anyone feeling poorly will be advised to adjust their steroid medications

accordingly ("sick day rules") and the study visit will be postponed until they are fully recovered. During the visit for parts A and B, the participant might feel unwell, particularly following the apomorphine injection. This is necessary to understand whether someone who is unwell can still effectively use an inhaler as rescue therapy (e.g. to control their breathing). If participants wish to stop the study early, hydrocortisone and nalaxone can be administered early to make them feel better, and this would not interfere with the measurement of inhaled fluticasone in the blood. However, the duration of nausea and vomiting with apomorphine is usually brief, around 20 to 30 minutes.
During part C of the study, the inhaled fluticasone will be given as an option for participants to try if they feel unwell or start to vomit. They do not have to use it, but we would like to understand if people find the inhaled route preferable to taking an injection, for instance, if they are vomiting. The risk is that they might delay an injection (a proven effective treatment) to wait for the effect of the inhaled steroid, about which we are unsure whether it will be effective. Participant diaries will have instructions about what to do in case of updosing, and the study team's contact details will be available so the participant can ring for advice.

What are the possible benefits and risks of participating?
The study is assessed as a low-risk CTIMP study. Inhaled fluticasone has been in widespread use for more than 30 years, with more than 4 million inhalers used by the NHS in England each year (PCA data, 2023). Inhaled fluticasone has an excellent safety record, with only occasional mild local side-effects such as oral candidiasis or dysphonia in heavy users. Inhaled fluticasone has been used for many years during pregnancy and standard of care NHS advice is to continue the medication during pregnancy. Therefore, patients who are trying to conceive or are pregnant will be excluded; however, pregnancy testing will not be routinely undertaken.
Potential benefits: Adrenal crisis remains the leading cause of death for young patients with adrenal insufficiency, and many patients feel either uncomfortable with self-injections of hydrocortisone or are frankly needle-phobic. This leads to a delay in administering ‘rescue’ glucocorticoid medication for people who are in a life-threatening situation. If the study shows that the fluticasone inhaler is effective and preferred as a rescue therapy by a proportion of adrenal insufficiency patients, then this could be a huge advantage which could have widespread application as the inhalers are widely available, have an excellent safety record and are inexpensive.
Potential detriments: During parts A and B, participants will have to undergo a temporary steroid withdrawal. We will make sure they are feeling well beforehand and they will have a contact number for a medically qualified member of the research team during the steroid withdrawal. Nevertheless, participants in previous studies with a similar steroid withdrawal protocol report feeling tired, fatigued or wanting to go to bed early on the evening of the steroid withdrawal. Although this seems like a significant risk, we have done more than 180 longer steroid withdrawals in previous studies of adrenal insufficiency patients without incident.
Part C: Studying stochastic but potentially life-threatening rare events is challenging, yet vitally important. To reduce any risk of harm during the study, participants will have the phone number of a member of the trial team to get immediate advice if they are feeling unwell. Participants will retain their usual rescue therapies, including oral hydrocortisone and IM injection vials. If they choose to use the inhaler and still feel bad 30 minutes after taking it, they will be advised to take the IM injection and call an ambulance, which is the usual standard of care. The highest risk of the study is that the inhaled fluticasone is ineffective, and participants waste their time using an ineffective treatment when they should have just injected themselves immediately. Another, lower, risk is that the convenience of up-dosing with fluticasone leads participants to over-treat themselves with steroid, leading to side-effects of steroid excess such as weight gain or easy bruising. However, this would be a short-term issue relevant only during the study period and unlikely to have long-term consequences over and above the chronic steroid dependency intrinsic to this participant group.

Where is the study run from?
Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
April 2025 to December 2027

Who is funding the study?
Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

Who is the main contact?
Simon Pearce, simon.pearce@ncl.ac.uk

Contact information

Type(s)
Scientific, Principal investigator

Contact name
Dr Simon Pearce

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Additional identifiers

Integrated Research Application System (IRAS)
1011661

Protocol serial number
11044

Study information

Scientific Title
Inhaled steroid as rescue therapy for patients with adrenal insufficiency: the INSTAR study

Acronym
INSTAR

Study objectives
In healthy people any stress on the body leads to an increase in the production of the stress hormone cortisol by the adrenal glands. However, in patients with adrenal insufficiency (AI) this ‘reflex’ release of cortisol is missing, which can lead to a life-threatening mismatch in the body’s

requirement for cortisol, known as adrenal crisis. The standard treatment for impending adrenal crisis is an emergency steroid injection, which is a life-saving intervention. However, many patients are reluctant to self-inject for adrenal crisis either because of needle-related anxiety, because the patient is not well enough to manage an injection, or the patient is too young to take agency for their own health. Easier and more familiar ways to administer steroids to prevent adrenal crisis would be welcomed by patients with AI. This project will entail three studies that will aim to operationalise inhaled steroids as a 'rescue' treatment in patients with AI, so this could be used in everyday NHS practice.

Objectives:
1. Determine whether inhaled fluticasone can attain sufficient tissue concentrations to be effective in averting or treating adrenal crisis
2. Determine whether someone feeling nauseated can use an inhaler effectively enough to deliver a therapeutic dose of fluticasone
3. Find out if people with adrenal insufficiency will accept and use a steroid inhaler as an alternative means to administer steroids
4. Determine patient wellbeing following fluticasone rescue as compared to hydrocortisone rescue
5. Determine patient acceptability of inhaler use when unwell
6. Determine if patients perceive the inhaler as a beneficial medication
7. Check metabolic safety (HbA1c, BMI, BP) of 6 months' inhaled fluticasone

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 15/05/2025, North East - Tyne & Wear South Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive , Newcastle upon Tyne, NE2 4NQ, United Kingdom; +44 (0)2071048120, +44 (0)207 104 8286; tyneandwearsouth.rec@hra.nhs.uk), ref: 25/NE/0087

Study design
Open randomized controlled cross over trial

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Adrenal insufficency

Interventions
Part A: 10 non-pregnant adult participants with primary adrenal insufficiency will attend the Newcastle clinical research facility fasted, first thing in the morning (e.g., 08:00 hours), having omitted their usual corticosteroid regimen for 14-18 hours (i.e., having taken their waking dose the previous day, but no subsequent doses). Participants will be allocated to receive either a standard dose of IM hydrocortisone (1 mg/kg or 100 mg, whichever is least) or 10 actuations of a fluticasone propionate (250 mcg metered dose Flixotide Evohaler) inhaler over 2 minutes, in a random order, 7-14 days apart. Participants will be asked to take a double dose of their regular

steroid replacement medication at the end of the treatment period (90 minutes), before discharge home, or earlier if the participant starts to feel unwell or there is a significant deterioration in vital signs (tachycardia, hypotension). A doctor will lead the visit and be present at all times until regular medication is given. After the oral hydrocortisone is given, the participant will be offered refreshments and observed for a further hour to make sure vital signs are stable and they are feeling well before a taxi back to home. The second visit for the comparator treatment will be offered between 7 and 14 days after the first visit. Following both visits for part A, 5 of the participants will be invited to take part in part B.

Part B encompasses just a single visit for 5 participants from Part A, who consent to participate in Part B. An identical protocol to part A will be followed, but after the t = -5 blood sampling, a subcutaneous dose of apomorphine (0.02 mg/kg) will be administered to induce nausea /vomiting, which usually ensues over 5-10 minutes. Once the nausea/vomiting has started, the participant will be asked to take the fluticasone propionate inhaler (250 mcg metered dose Flixotide Evohaler, 10 actuations) and serum will be drawn for testing every 10 minutes for 30 minutes, then at 45, 60 and 90 minutes for measurement of fluticasone levels. We will compare these to the equivalent levels taken from Part A, performed without the emetogenic stimulus. The test will be terminated at 90 minutes with IV hydrocortisone (100 mg) with or without IV naloxone (0.4 mg) according to participant feelings of nausea, or earlier if the participant starts to feel unwell or there is a significant deterioration in vital signs (tachycardia, hypotension). After the hydrocortisone +/- naloxone is given, the participant will be offered refreshments and observed for a further hour to make sure vital signs are stable and they are feeling well before a taxi back to home.

Part C: involves a 6-month field trial of inhaled fluticasone propionate (250 mcg metered dose Flixotide Evohaler, 10 actuations) as rescue therapy for patients with either primary adrenal insufficiency (Addison's disease and bilateral adrenalectomy) and secondary ACTH deficiency owing to pituitary tumours, pituitary radiotherapy or pituitary surgery, who will be recruited from NHS clinics. Following written, informed consent, participants will be asked to fill in three short questionnaires concerning their general wellbeing (WHO-5), health state (EQ-5DL) and disease-specific QoL (AddiQoL). Data that are routinely gathered at NHS clinic visits for this patient group, including BMI, blood pressure and HbA1c, will be noted. Patients will be given education about how to use the fluticasone inhaler, including a video and an observed actuation trial and an inhaler will be dispensed. A diary to record any episodes of up-dosing, including inhaler use and incipient or actual adrenal crisis, will be kept. Participants will have a contact email for the study team in case they need to contact them to discuss inhaler use or any complications. Routine contact will be made with the participant after 4 weeks to check whether they have used the inhaler and any questions about such use. At the end of 6 months, patients who found the inhaler most useful and least useful will undergo a 30-minute structured interview concerning the utility of the inhaler in their day-to-day adrenal insufficiency management. Routine clinical parameters will be recorded again, including BMI, blood pressure and HbA1c. After 6 months, the study will be complete, but the participants will be allowed to keep the inhaler if they find it has been helpful.

The end of the study is defined as the Last Patient, Last Visit. Participants who find the inhaled fluticasone a useful adjunct for management of their adrenal insufficiency may opt to keep the inhaler or have a new one prescribed. Results of the study will be communicated directly to participants at the end of the study, and by digital media of the Addison's disease self-help group (patient support organisation). Ongoing NHS care will be with the regular Friday adrenal clinic or other NUTH endocrine clinic, as appropriate.

Sequence randomisation will be done using a prespecified order generated through the Sealed Envelope web randomisation service and kept securely in the trial master file.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Flixotide 250 Evohaler [fluticasone propionate], hydrocortisone succinate

Primary outcome(s)
Part A: Plasma ACTH measured using immunoassay at 10, 20, 30, 45, 60, 90 min following inhaled fluticasone vs IM hydrocortisone bolus
Part B: Serum fluticasone levels measured using mass spectrometry at 10, 20, 30, 60 min following inhaled fluticasone in participants with drug-induced nausea/vomiting
Part C: Utilisation of fluticasone in real-life situations measured using diary analysis and narrative review at end of study; 6 months

Key secondary outcome(s))
Part A:
1. Serum fluticasone and/or cortisol levels measured using mass spectrometry and immunoassay, respectively, at 10, 20, 30, 60 min following inhaled fluticasone or IM hydrocortisone bolus
2. Biochemical analysis of stress markers: prolactin, copeptin, IL6, TNFa, GDF15, miRNA122-5b measured using immunoassay at 10, 20, 30, 60 minutes
3. Patient health state assessed using visual analogue scales at 20, 40, 60 and 90 minutes
4. Qualitative patient feedback on experience using interview at end of study
5. Vital signs measured using dynamap at 10, 20, 30 and 60 minutes

Part B:
1. Patient health state assessed using visual analogue scales at 20, 40, 60 and 90 minutes
2. Qualitative patient feedback on experience using interview at end of study
3. Vital signs measured using dynamap at 10, 20, 30 and 60 minutes

Part C:
1. Patient-reported wellbeing outcome(s) measured using WHO-5, AddiQoL and EQ-5D at end of study (6 months)
2. Patient-reported acceptability of inhaled steroid measured using Treatment Satisfaction Questionnaire for Medication (TSQM) at end of study (6 months)
3. Blood pressure, BMI and serum HbA1c measured using SECA scale, dynamap and immunoassay, respectively, at end of study (6 months)

Completion date
31/12/2027

Eligibility

Key inclusion criteria

1. Patients with primary adrenal insufficiency (owing to Addison’s disease or bilateral adrenalectomy)
2. Age over 18 years
3. Ability to give written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Not pregnant, breastfeeding or with a plan for pregnancy within 1 month
2. No known residual adrenal function, documented poor medication concordance or persistent pigmentation, concomitant type 1 diabetes (for Parts A + B only)
3. No significant lung disease that could impair the absorption of fluticasone
4. No active ischaemic heart disease, cerebrovascular disease or other condition that, in the opinion of the principal investigator, would render the temporary suspension of steroid hormone unsafe
5. No dementia, active psychotic or serious mental health condition
6. No current use of steroid inhaler or other medication that could interfere with the interpretation of plasma ACTH, including opiates, non-replacement steroids (e.g., topical or depot), ritonavir, other potent CYP3A4 inhibitors
7. No known allergy or anaphylaxis to fluticasone or any other component of the investigative product
8. Not participating in another CTIMP study, currently or within the prior 8 weeks

Date of first enrolment
20/06/2025

Date of final enrolment
31/12/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
United Kingdom
NE1 4LP

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Newcastle upon Tyne Hospitals NHS Foundation Trust

Alternative Name(s)
Newcastle upon Tyne Hospitals NHS Trust

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Anonymised IPD will be made available to bona fide researchers upon request, following a data access committee review and the signing of a data use agreement. The Newcastle University secure data repository will host the data download following cleaning and analysis at the end of the study.

IPD sharing plan summary

Available on request