ISRCTN67193733 https://doi.org/10.1186/ISRCTN67193733

# The Pulses Study

| Submission date | Recruitment status | [X] Prospectively registered |
|---|---|---|
| 03/12/2014 | No longer recruiting | [_] Protocol |
| **Registration date** | **Overall study status** | [_] Statistical analysis plan |
| 03/12/2014 | Completed | [X] Results |
| **Last Edited** | **Condition category** | [_] Individual participant data |
| 20/10/2023 | Nutritional, Metabolic, Endocrine | |

## Plain English summary of protocol

Background and study aims
Cortisol (also called hydrocortisone) is a hormone produced by the adrenal glands that is essential for life. It is produced in a daily (circadian) rhythm with high levels first thing in the morning, falling to very low levels at night time. There are many medical conditions such as Addison's disease, congenital adrenal hyperplasia (CAH) and pituitary disease where patients cannot produce enough of this hormone and therefore need replacement therapy. At present patients are given standard replacement therapy with tablets in an attempt to mimic a normal hormonal profile. However, despite this, their death rates remain twice that of the general population (similar to the increased risk from smoking) and patients often feel generally unwell with severe fatigue (tiredness). It is now known that cortisol is released into the blood stream in pulses, and that this pattern is vital for the body's normal responses. Unfortunately this pulsatile pattern is not the pattern of replacement that is currently given and this could contribute to the excess death rate and poor quality of life of these patients. At the University of Bristol researchers have developed a system using a commercially available infusion pump that can deliver pulses of hydrocortisone under the skin in a way that closely mimics natural hormone release. They want to use this to compare the hormonal responses of patients with Addison's disease and congenital adrenal hyperplasia on standard oral and pulsatile subcutaneous hydrocortisone replacement therapy.

Who can participate?
Adults aged 18-64 years that are right handed and have been diagnosed with Addison’s disease and CAH.

What does the study involve?
Participants are randomly allocated into one of two groups. Those in group 1 receive their standard dose of oral medications (tablets) and a placebo infusion via an automated pump for six weeks. Those in group 2 receive an oral placebo and pulsatile hydrocortisone via the pump for six weeks. The pump must be worn 24 hours a day (although can be taken off for showering etc.) and the syringes in the pump need changing twice a week. Participants are taught how to do this, but until confident must see a study investigator twice a week (this can be done at a location convenient to the patient) to have their syringe and line changed. After the initial six week period, the participants swap treatments, so those in group 1 are treated as if they were in group 2 and vice versa for a further six weeks. The researchers look at how well the different treatments work by measuring hormone levels before the start of treatment then again after

each six week treatment period. The participants metabolic profile, quality of life and energy and activity levels are also tested regularly throughout the study period. The participants mental (cognitive) abilities and emotional health are measured using psychological tests and MRI scanning in week six of each treatment period, which are specifically tailored to the symptoms of each individual.

What are the possible benefits and risks of participating?
The benefits of taking part is that it will help researchers understand if it is the lack of pulsatile hormone replacement that is contributing to patients symptoms and improve their knowledge on how steroids can cause side effects. The main risk of taking part is the potential of having an adrenal crisis. Participants are therefore asked a carry an emergency kit with them at all times and stay local to the Bristol area whilst on the trial.

Where is the study run from?
University of Bristol (UK)

When is the study starting and how long is it expected to run for?
November 2014 to August 2022 (updated 20/06/2019, previously: June 2018)

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Dr Georgina Russell

# Contact information

### Type(s)
Scientific

### Contact name
Dr Georgina Russell

### Contact details
University of Bristol
Dorothy Hodgkin Building
Whitson Street
Bristol
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BS1 3NY

# Additional identifiers

### EudraCT/CTIS number
2012-001104-37

### IRAS number

### ClinicalTrials.gov number

### Secondary identifying numbers
17145

# Study information

### Scientific Title
Pulsed glucocorticoid replacement therapy for patients with adrenocortical insufficiency secondary to Addison’s disease and congenital adrenal hyperplasia

### Study objectives
1. To compare the hormonal responses of patients with Addison's disease and congenital adrenal hyperplasia on standard oral and pulsatile subcutaneous hydrocortisone replacement therapy.
2. To compare the metabolic, psychological (cognitive and emotional processing) and quality of life measures of patients with Addison's disease and congenital adrenal hyperplasia on standard oral replacement and pulsatile subcutaneous hydrocortisone replacement therapy.

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
NRES Committee South West - Central Bristol, 06/10/2014, ref: 14/SW/1050

### Study design
Randomised, interventional

### Primary study design
Interventional

### Secondary study design
Randomised controlled trial

### Study setting(s)
Hospital

### Study type(s)
Treatment

### Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

### Health condition(s) or problem(s) studied
Topic: Metabolic & Endocrine; Subtopic: Metabolic & Endocrine; Disease: Metabolic & Endocrine

### Interventions
Patients will receive hydrocortisone in a double blinded randomised cross over fashion either:
1. Their standard dose of oral hydrocortisone (over encapsulated) for 6 weeks and a placebo subcutaneously via an automated pump
2. A comparative oral placebo and hydrocortisone (same dose as usual oral dose) subcutaneously

via a portable infusion pump.
The infusion pump shall deliver either the hydrocortisone or placebo (normal saline) continuously over a 24 hour period as discrete pulses.

### Intervention Type
Drug

### Phase
Not Applicable

### Drug/device/biological/vaccine name(s)
Hydrocortisone

### Primary outcome measure
Current primary outcome measure as of 24/02/2021:

Cognitive and emotional outcome of the P1 vital Emotional test battery at week 6.

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Previous primary outcome measure:

Physiological cortisol profiles with adequate suppression of ACTH in all patients and 17-OHP in CAH patients using subcutaneous pulsatile hydrocortisone replacement. Timepoint(s): baseline and 6 weeks

### Secondary outcome measures
Current secondary outcome measures as of 24/02/2021:

1. Anthropometric assessments (weight, blood pressure, body composition) at baseline and then weekly for the duration of the study
2. Fasting metabolic blood samples (HbA1c, lipids, osteocalcin, insulin resistance) at baseline and week 6
3. 24 hour blood sampling study for cortisol, ACTH (AD and CAH) and 17-OHP (CAH only) at week 6 (optional participation)
4. Quality of life and mood was assessed using the Short Form 36 Health Survey (SF-36), Chadler Fatigue Scale (CFS), the Identity Consequence Fatigue Scale (ICFS), the Addison's specific Disease QOL Score (AddiQoL), Positive and Negative Affect Score (PANAS) at baseline, week 1, and week 6, and ecological momentary assessment (EMA) for the duration of the study
5. Sleep was assessed using the Pittsburg Sleep Quality Index (PSQI) and Leeds Sleep Questionnaire (LSQ) at baseline, week 1, and week 6, and actigraphy for the duration of the study
6. Emotional processing was assessed at week 6 using the Emotion Potentiated startle Response (EPSRT) and functional MRI
7. Working memory was assessed using the N-Back at week 1 and 6

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Previous secondary outcome measures:

1. Cognitive: Timepoint(s): 6 weeks
2. EMA: Timepoint(s): time -1, 0, 1, 2, 3, 4, 5, 6, 7 weeks;
3. Fatigue: Timpoint(s): baseline and 6 weeks;
4. Metabolic profile: Timepoint(s): baseline and 6 weeks

### Overall study start date
03/11/2014

### Completion date
14/08/2022

## Eligibility

### Key inclusion criteria
1. Male and female patients with confirmed Addison's disease and CAH
2. Aged 18 to 64 years
3. Females of child bearing potential must be using a highly effective method of contraception / birth control as defined in ICH (M3) if sexually active
4. Right handed
5. Able to give informed consent

### Participant type(s)
Patient

### Age group
Adult

### Lower age limit
18 Years

### Sex
Both

### Target number of participants
Planned Sample Size: 20; UK Sample Size: 20

### Total final enrolment
21

### Key exclusion criteria
1. Any significant current cerebral, cardiovascular, respiratory, hepatobiliary, pancreatic disease, renal dysfunction, gastrointestinal emptying or motility disturbances.
2. No current treatment or within the last 3 months of another underlying disease that could necessitate treatment with glucocorticoids
3. Taking of medications that interfere with cortisol metabolism (antiepileptics, St Johns wart, rifampicin)
4. Diagnosis of Addison's disease less than 6 months ago
5. Pregnant or lactating women
6. Greater than 21 units of alcohol per week

7. Taking of any investigational drug within the past two months
8. Known allergy to any of the study medications and /or materials used in the pump
9. Needle phobia
10. Contraindication to fMRI scan i.e. metal implant/shrapnel
11. Claustrophobia
12. Left handed/significant ambidexterity
13. Dyslexia

### Date of first enrolment
05/12/2014

### Date of final enrolment
14/08/2017

## Locations

### Countries of recruitment
England

United Kingdom

### Study participating centre
**University of Bristol**
Dorothy Hodgkin Building
Whitson Street
Bristol
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BS1 3NY

## Sponsor information

### Organisation
University Hospitals Bristol NHS Foundation Trust

### Sponsor details
Research & Development
Upper Maudlin Street
Bristol
England
United Kingdom
BS2 8AE

### Sponsor type
Hospital/treatment centre

### ROR

https://ror.org/04nm1cv11

# Funder(s)

**Funder type**
Government

**Funder Name**
Medical Research Council

**Alternative Name(s)**
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

**Funding Body Type**
Government organisation

**Funding Body Subtype**
National government

**Location**
United Kingdom

# Results and Publications

**Publication and dissemination plan**
Not provided at time of registration

**Intention to publish date**
14/08/2023

**Individual participant data (IPD) sharing plan**

**IPD sharing plan summary**
Not expected to be made available

**Study outputs**

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| HRA research summary | | | 28/06/2023 | No | No |
| Results article | | 19/10/2023 | 20/10/2023 | Yes | No |