UK Heart Failure with Preserved Ejection Fraction Registry (UK HFpEF)

UK HFpEF Study Reference Manual v1.5 01/07/25

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2 Purpose

The purpose of this study reference manual is to provide supplementary guidance for some of the activities and procedures that take place during the UK HFpEF study. It does not replace the study Protocol. The study Protocol is the overriding document.

3 Website and useful contacts

A full list of contacts is provided in the study Protocol.

3.1 Website

The study website is found at ukhfpef.org

The website contains:

- Information for patients, including the Participant Information Sheet and Consent form and a video about the study. Please encourage participants/potential participants to access the website.
- Information for the research team, including the Participant Information Sheet and Consent form, study posters and contact details for the central UK HFpEF research team.
- The link to the study database
- Study progress tracker, including number of participants and open sites.

3.2 Contacts

3.2.1 Central UK HFpEF research team

The central study team includes Angela Branson (study manager), Lucy Priestner and Fardad Soltani (research fellows) and Chris Miller (chief investigator). Please get in contact about any study related matter using the following email address:

UK-HFpEF@mft.nhs.uk

In addition, please feel free to contact Angela or Chris directly:

3.2.2 Study manager

Angela Branson

Manchester University NHS Foundation Trust

Email: Angela.Branson@mft.nhs.uk

Phone: 0161 291 4075

3.2.3 Chief Investigator

Chris Miller

Manchester University NHS Foundation Trust

Email: christopher.miller@manchester.ac.uk

Phone: 0161 291 3244

4 Participant Identification Code

Each participant will have a unique Participant Identification Code.

The code is made up of three parts, as follows:

- Study reference: HF
- Site code: Each site will be assigned a 2-letter code. Sites will be informed of this during their Site Initiation Visit
- Participant number: Each participant will be assigned a 4-digit number

i.e., **HF–Site identification code–Participant number**

There should be dashes between the different sections of the Participant Identification Code and no spaces.

For example:

- The Participant Identification Code for participant 0032 recruited in Manchester (site code MN) would be: **HF–MN–0032**
- The Participant Identification Code for participant 0124 recruited in Leicester (site code LE) would be: **HF–LE–0124**
- The Participant Identification Code for participant 0124 recruited in Manchester (site code MN) would be: **HF–MN–0124**

5 Blood sampling at sites

Blood sampling will be performed for storage of plasma, serum, buffy coat and DNA, in order to conduct a range of 'omic analyses. Blood samples will be sent to the NIHR National Biosample Centre (UK Biocentre) for processing and storage.

Please ensure that you are familiar with all of this section before recruiting the first participant.

5.1 Blood sample collection kits

- For each participant at each site, a PathoShield box containing the necessary equipment for blood sampling and posting will be provided. Each box will include:
    - x2 EDTA Vacutainer 10.0 ml
    - x1 Serum Vacutainer 8.5 ml
    - 21G butterfly needle and connector
    - Sample bag and PathoShield Box security seal
    - 6 barcoded labels unique to that participant
    - Sample linkage form
- Please only use the Vacutainers we supply as the UK Biocentre are only able to process these specific ones. The shipments to sites include spare EDTA and Serum Vacutainers. If you require more, please email Angela.Branson@mft.nhs.uk

Each box should only be used for one participant

5.1.1 PathoShield Box

- The PathoShield box will be labelled with the UK Biocentre address and a pre-paid postage label.

5.1.2 Vacutainer Collection Tubes

- For each participant, blood should be collected into the x2 EDTA and x1 Serum vacutainer tubes that are provided (see Table 1 below), using the provided 21G butterfly needle and connector.
- Please aim to fill each vacutainer tube completely, and please fill the vacutainers in the following order to facilitate maximum utility of the samples for analysis:

  EDTA 1 → Serum → EDTA 2

  i.e. please fill the first EDTA tube before moving onto the Serum tube, and then fill the Serum tube before moving onto the second EDTA tube.
- If it is not possible to fill all of the tubes, please send the tubes that you have managed to draw blood into.
- Record the time the samples were taken.

Table 1

Tube	Usual appearance	Number of tubes
EDTA	Purple top 	2 x 10.0 ml
Serum	Gold or red top 	1 x 8.5 ml

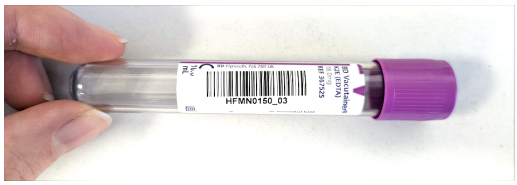
5.1.3 Butterfly needle and connector

- One 21G (green) butterfly needle and connector will be provided in each PathoShield box.
- Should blood draw fail and a repeat attempt is required, please use local blood draw equipment.

5.1.4 Barcoded labels

- 6 barcoded labels will be provided per participant in each PathoShield box. Each barcoded label will contain the participants unique participant ID number, with a suffix of _01 to _06. Example barcoded labels are shown below:

- One barcoded label should be attached to each of the following (it doesn't matter which label of the 6 labels is used for each):
    - Each of the two EDTA vacutainer tubes
    - The serum vacutainer tube
    - The sample linkage form (see section 5.1.6)
- The remaining 2 barcoded labels are provided as spares.
- The barcoded labels should be applied to the blood tubes as below to ensure they can be read by the lab machines:



5.1.5 Put labelled samples into sample bag

- Put the three barcode labelled blood tubes into the sample bag provided and place inside the PathoShield box.

5.1.6 Complete the sample linkage form

- A sample linkage form will be provided in each PathoShield box. See Appendix for what this looks like.
- Complete all sections of the sample linkage form.
- Make sure to attach a barcoded label to the form.
- Place the sample linkage form inside the PathoShield box.

5.1.7 Close and seal the PathoShield Box

- Close the PathoShield box and seal with the security seal that is provided in the box (picture below).

5.1.8 Post the PathoShield box to UK Biocentre

- Please put the PathoShield box in the post.
- Please ensure that it is posted on the same day as collection. If this is not possible, the PathoShield box should be stored in the fridge overnight and sent the following day.
- It is posted via Royal Mail i.e. a courier is not required.

5.1.9 UK HFpEF Database

- In the database, select the Participant and go to the ‘Sample Details’ page.
- Complete all sections which mirror the Sample Linkage form.

6 Central sample repository

Long term sample storage will be in the UK Biocentre (https://www.ukbiocentre.com/), which is based in Milton Keynes and is where the samples for other large cohorts, such as the NIHR Bioresource, are stored.

6.1 Contact

Rachel Johnston

rachel.johnston@ukbiocentre.com

6.2 Sample auditing

1. The central UK HFpEF team will regularly liaise with the UK Biocentre team to monitor samples being received and will audit these against information included in the database.
2. The UK HFpEF team will feedback regularly to sites regarding this.
3. Please ensure sample data is entered correctly in the database and on the sample linkage form.

7 New York Heart Association (NYHA) Class

- **Class I:** No limitation of ordinary physical activity.

  The participant does not develop symptoms during ordinary physical activity, such as walking or climbing stairs. (The participant may develop symptoms during strenuous exertion and still be in Class I).

- **Class II:** Slight limitation of physical activity.

  The participant develops symptoms on walking for more than 100 metres on the flat at normal pace or on climbing more than one flight of ordinary stairs at normal pace.

- **Class III:** Marked limitation of physical activity.

  The participant develops symptoms on walking short distances, such less than 100 metres on the flat at normal pace, or on climbing 1 flight of ordinary stairs at normal pace.

- **Class IV:** Unable to carry out any physical activity without symptoms.

  The participant is unable to carry out any physical activity without developing symptoms, or has symptoms at rest.

Symptoms refer to breathlessness, fatigue or palpitations.

8 Clinical Frailty Scale

Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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9 Patient reported outcome measure

Sites should use Kansas City Cardiomyopathy Questionnaire (KCCQ).

See Appendix.

(Minnesota Living with Heart Failure Questionnaire (MLHFQ) was used originally, but should no longer be used).

10 Six minute walk test

Six-minute walk testing (6MWT) should be performed if site logistics and participant characteristics allow.

The information below is a suggested guide although sites may follow their own procedure, provided it does not differ substantially.

Set-up

- Flat, straight corridor
- Turnaround points marked, with the distance between the points known (ideally 30 metres, with metre wall marks)
- Timer
- Participants should wear comfortable clothes and shoes, and use their usual walking aids

Procedure

- Participants should rest prior to the test i.e., no warm-up
- Provide the following instructions:

  "The object of this test is to walk as far as possible for 6 minutes. You should walk back and forth along the corridor. You should turn around briskly. Don't run or jog.

  You may slow down, or stop, if necessary, but please resume walking as soon as you are able.

  I will inform you of the time remaining, and provide encouragement, each minute.

  Please do not talk during the test unless there is a problem. If you experience chest pain or light-headedness, please stop and let me know.

  When six minutes are up, I will ask you to stop where you are.

  Do you have any questions?"
- You can demonstrate by walking one lap yourself
- To begin the test, ask the participant to stand on the starting line, and say: "Start now, or whenever you are ready". Start a timer when walking starts. Do not walk with the participant.
- Say the following standardised encouragement statements at one minute intervals:

  At 1 minute: "You are doing well. You have 5 minutes to go."

  At 2 minutes: "Keep up the good work. You have 4 minutes to go."

  At 3 minutes: "You are doing well. You are halfway done."

  At 4 minutes: "Keep up the good work. You have only 2 minutes left."

  At 5 minutes: "You are doing well. You have only 1 minute to go."

  At 6 minutes: "Please stop where you are."
- If the participant stops during the test, keep the timer running, and say: "Please continue walking whenever you feel able"
- If the participant is not able to continue (or if you decide that they should not continue), stop the timer, wheel a chair over for them to rest in, note the distance walked, the time stopped and reason for stopping

End of the test

- At the end of the test, mark the spot where the participant stopped and measure to the nearest metre
- Record the overall distance to the nearest metre

11 Echo protocol

A standardised echo protocol is recommended, in line with the British Society of Echocardiography Minimum Dataset.

Echo data uploaded to the study database should be taken from an echo performed within 2 years of the study visit.

See Appendix.

12 CMR protocol

A standardised cardiovascular magnetic resonance (CMR) protocol is recommended.

See Appendix.

13 Data entry

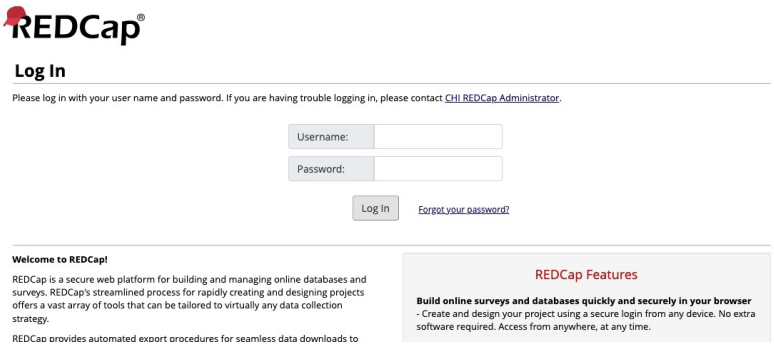
Study data should be entered into the UK HFpEF study database. The data is stored in a secure Trusted Research Environment.

13.1 Logging in

Please go to the UK HFpEF website: ukhfpef.org

Please click on the Research Team tab at the top right of the page.

Please click on the link to access the study database. This will take you the following page:



The central UK HFpEF team will provide usernames and passwords to the research team at your site as part of the site initiation process.

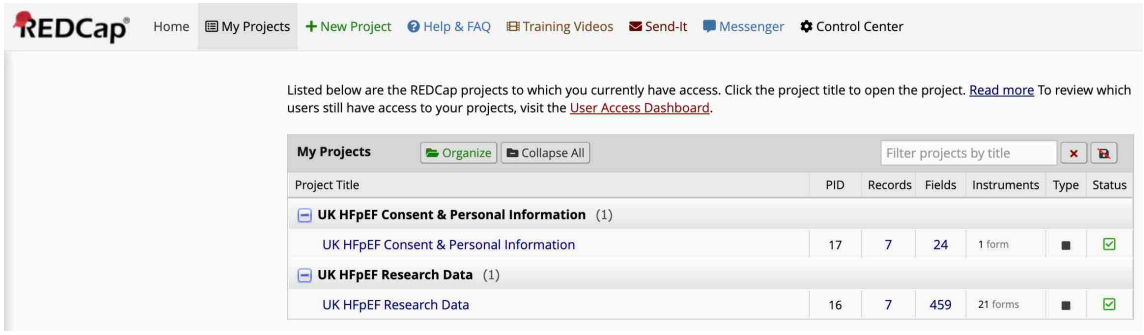
Please enter your username and password and click Log In.

This will bring you to the page shown below. If you cannot see this page, click on the “My projects” tab at the top of the screen, which should bring you to this page.

There are two separate databases; “UK HFpEF Consent & Personal Information” which stores participant consent and personal information, and “UK HFpEF Research Data” which stores all other pseudonymised information.

Start by clicking on the “UK HFpEF Consent & Personal Information” database and enter the participant consent and personal information. Next click on the “UK HFpEF Research Data” and enter the study information.

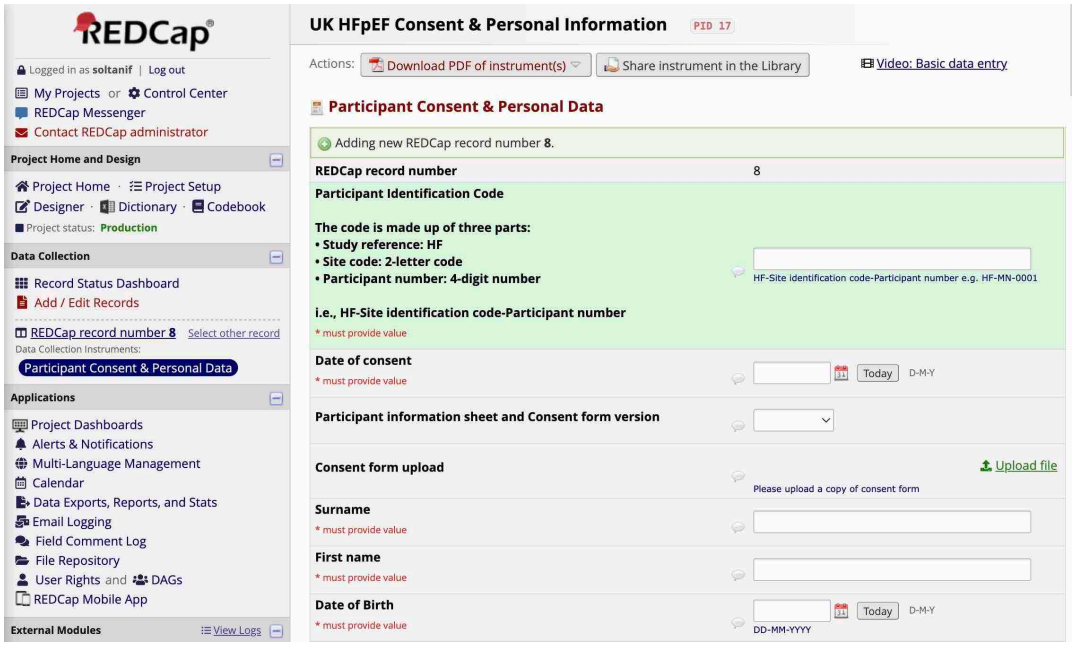
Please ensure that the Participant Identification Code entered in the “UK HFpEF Consent & Personal Information” database matches the Participant Identification Code entered in the “UK HFpEF Research Data” database.



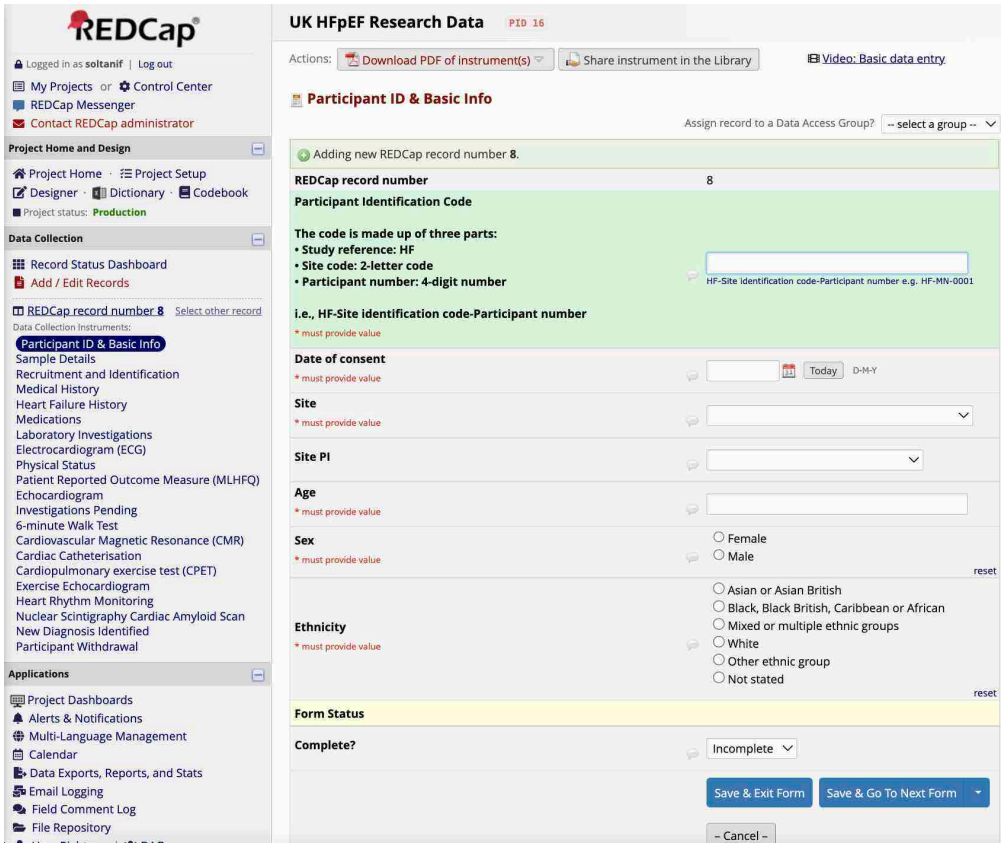
13.2 Adding a new participant

To add a new participant please select “Add / Edit Records” in the left-sided toolbar (red text) followed by “Add new record” (green).

Begin data entry for each participant by completing the “Participant Consent & Personal Data” page within the “UK HFpEF Consent & Personal Information” database. Once this is complete, click “Save & Exit Form” at the bottom of the page.



Continue data entry for each participant by entering the “UK HFpEF Research Data” database. Click on the grey icon next to “Participant ID & Basic Info”. Once each section is complete, please move on to the next section by clicking “Save & Go To Next Form” at the bottom of each page or by selecting the relevant section on the left-sided panel.

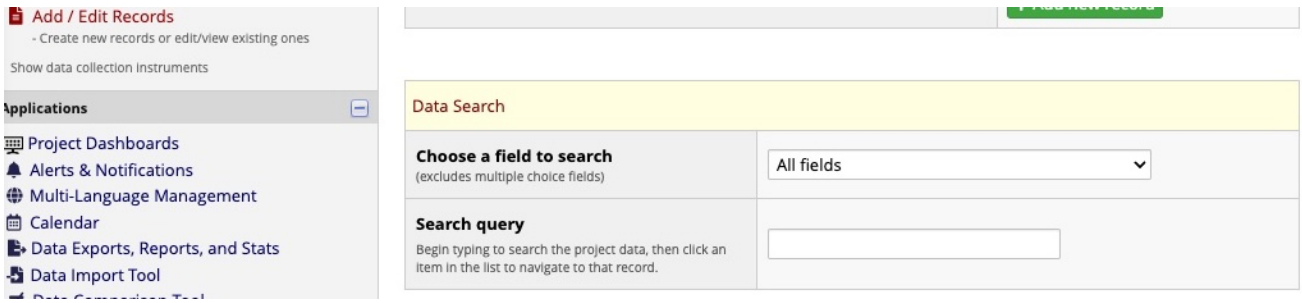


13.3 Editing an existing participant record

To edit an existing participant record please select “Add / Edit Records” on the left-sided panel.

There are then multiple ways to find the relevant participant record.

The easiest way to do this is using the “Data Search”. Next to the “Choose a field to search”, please select “All fields” or “participant_id” from the dropdown menu. Following this please enter the relevant study ID number in the “Search query” box and select the relevant record.

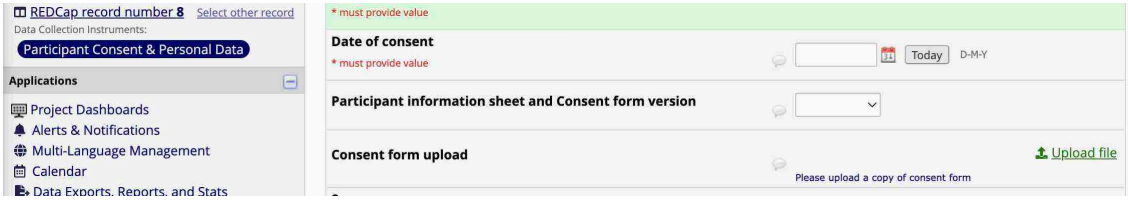


13.4 Uploading consent form and ECG

A copy of the participant consent form and pseudonymised ECG should be uploaded directly to REDCap within each participant record.

13.4.1 Consent form

On the Participant Consent & Personal Data section in the "UK HFpEF Consent & Personal Information" database, click on the Upload file to upload the consent form.



13.4.2 ECG

On the Electrocardiogram (ECG) section in the "UK HFpEF Research Data" database, click 'Yes' to "ECG available to upload to study database?" and click on the Upload file to upload the ECG. Please ensure no participant details are on the ECG, except the participant identification code.

13.5 Uploading echocardiograms and CMR scans

Upload of echocardiograms and CMR scans (i.e., the raw image files (DICOM)) is via a file transfer system called ownCloud that is built into the database. A file transfer system is required due to file size.

The process is the same for echocardiograms and for CMR scans, however, **echocardiograms should be uploaded via the echocardiogram database section, and the CMR scans should be uploaded via the CMR database section.**

Please ensure that echocardiograms and CMR scans are pseudonymised before uploading.

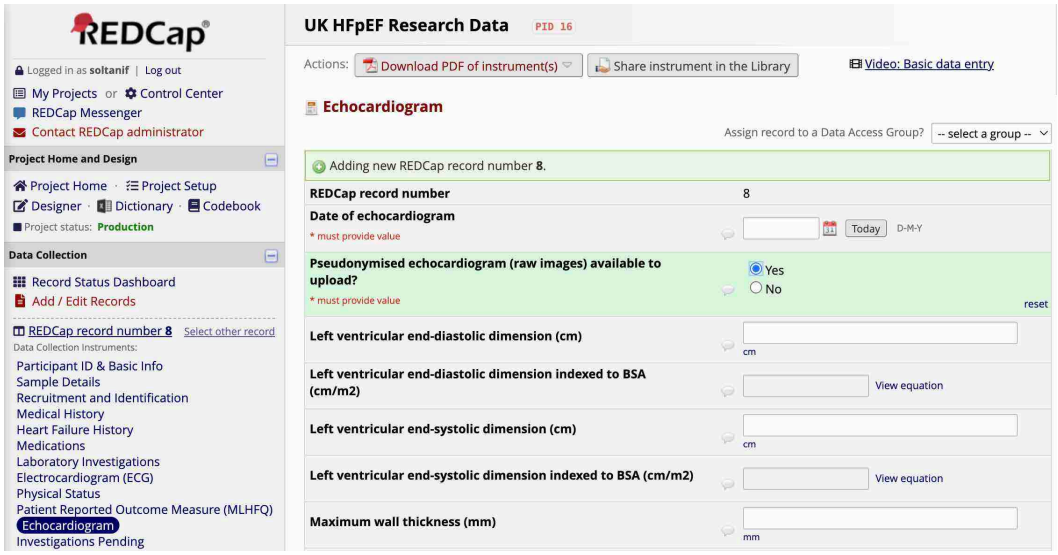
Please save the participant's echocardiogram in a folder, named as the participant's study ID with a suffix 'echo' (e.g., HF-MN-0001_echo).

Please save the participant's CMR in a separate folder, named as the participant's study ID with a suffix 'cmr' (e.g., HF-MN-0001_cmr).

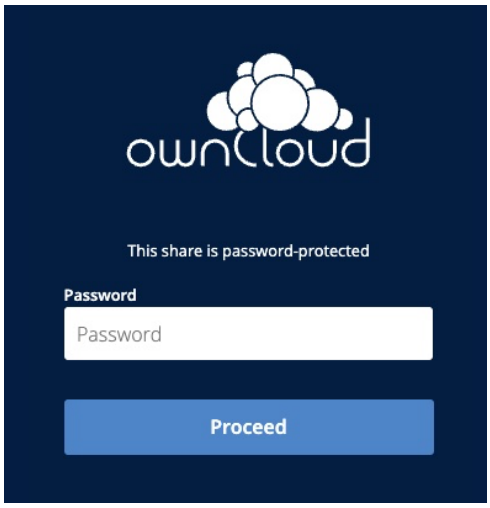
The instructions below are for uploading an echocardiogram. The process is the same for uploading a CMR scan, **except the CMR scan should be uploaded via the CMR database section.**

In the echocardiogram section, click 'Yes' to "Pseudonymised echocardiogram (raw images) available to upload?"

Copy and paste the link into a new tab or browser to take you to the ownCloud file transfer page.

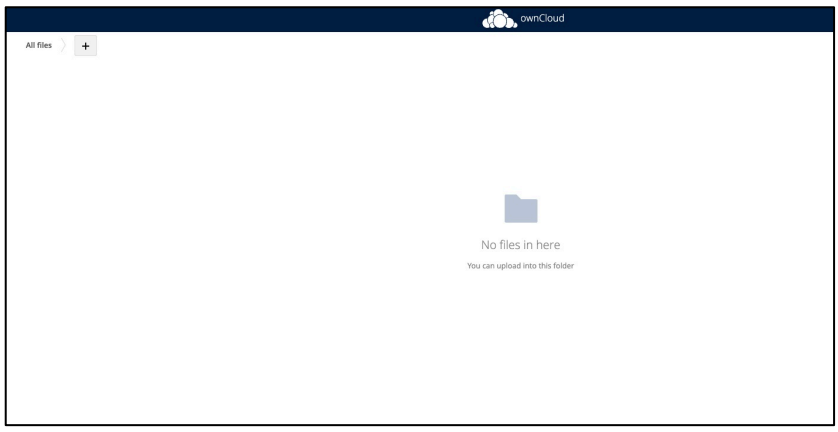


This will take you to the page shown below. The central UK HFpEF team will provide passwords to the research team at your site as part of the site initiation process.



Please enter the password and click Proceed.

This will take you to the File upload page as shown below.



To start the upload, the folder containing the participant's echocardiogram should be 'drag and dropped' into the centre of the page (i.e. over the light blue folder in the image above).

Once you have uploaded a folder, please close the tab.

Please note: Echocardiogram and CMR DICOM are uploaded to separate storage areas. Please only upload the echocardiogram using the link in the echocardiogram database section i.e., do not also try to upload the CMR scan via the echocardiogram section. Please upload the CMR scan using the link in the CMR database section.

14 Data field notes

- The data fields are as set out in the database.
- There are core ECG and echo data that should be entered into the database. Please also upload the ECG pdf and raw echo DICOM (mandatory).
- Patients with HFpEF often undergo investigations or procedures such as cardiac catheterisation, cardiopulmonary exercise testing (CPET), exercise echo, heart rhythm monitoring, nuclear scintigraphy cardiac amyloid scanning. If participants do have any of these investigations or procedures, please record the data in the relevant database section.
- If a specific diagnosis is identified after undertaking additional investigations, please record this in the relevant section.

15 Participant withdrawal

1. See Protocol section ‘15.5 Withdrawal’.
2. In the UK HFpEF database, select the participant and go to the ‘Withdrawal’ page.
3. Select the withdrawal option that the participant has chosen i.e. (see Protocol for details):
    1. No further contact.
    2. No further contact and no further analysis of sample/s.
    3. No further contact and no further research using samples or information.
4. Where the participant’s preference cannot be confirmed, select ‘1. No further contact.’ This is as explained in the Participant Information Sheet and the Protocol.
5. Email Angela Branson, study manager (UK-HFpEF@mft.nhs.uk), stating the Participant Identification Code and the withdrawal option.

16 Ordering study materials

If you require more storage boxes and barcode tubes, or any other study materials, please email UK-HFpEF@mft.nhs.uk with the details.

Please allow 2-3 weeks for delivery.

17 Appendices

17.1 Appendix 1. Sample Linkage Form

17.2 Appendix 2. Kansas City Cardiomyopathy Questionnaire (KCCQ)

17.3 Appendix 4. Echo protocol

17.4 Appendix 5. CMR protocol