# The Anti-Freaze-F Study - "Anti-TNF for treatment of frozen shoulder" - a feasibility study

<b>Submission date</b> 07/09/2021	Recruitment status Stopped	[X] Prospectively registered		
		[X] Protocol		
Registration date	Overall study status	Statistical analysis plan		
21/12/2021 Last Edited	Stopped  Condition category	[X] Results		
		☐ Individual participant data		
17/05/2024	Musculoskeletal Diseases	<ul><li>Record updated in last year</li></ul>		

## Plain English summary of protocol

Current plain English summary as of 29/03/2022:

#### Background and study aims

Frozen shoulder is a common condition affecting approximately 9% of people aged 25-64 years. During the early phase the pain is usually unbearable and the later restriction in movement is severely limiting. It occurs when the flexible tissue (capsule) that surrounds the shoulder joint becomes inflamed, thickened and tight. The pain can be very severe and lasts 3-9 months, followed by a 4-12 month period of increasing stiffness, after which the condition usually improves. Frozen shoulder often affects a person's ability to sleep, carry out everyday activities, and work. Current treatments include rest, painkillers, anti-inflammatories, physiotherapy and steroid injections. If stiffness persists, surgery is sometimes recommended. However, there is no evidence that any of these treatments lead to significant benefit in the long term, with many being ineffective.

The aim of this study is to find out if it is possible to run a larger study to test whether an injection of adalimumab can reduce pain and prevent the disease from getting worse, if given during the early painful phase of frozen shoulder. We need to conduct this smaller study first to be sure it's possible to identify and treat people with early stage frozen shoulder, before we conduct a much larger study to find out if this treatment works.

#### Who can participate?

In this study the investigators will include 84 adults from 5 sites with painful early stage frozen shoulder who have not yet received treatment.

#### What does the study involve?

People will be randomised to receive either an injection of the drug adalimumab or a dummy injection of saline (placebo) directly into the shoulder joint, both guided by ultrasound. All participants will also receive standardized advice on how to manage their shoulder pain. The investigators will assess participants before treatment and three months later. Adalimumab has been used very successfully to treat other inflammatory diseases such as rheumatoid arthritis.

What are the possible benefits and risks of participating?

We hope the information we obtain from this study will be used to help treat people with frozen shoulder problems more effectively.

There is a possibility you will be harmed by this treatment, although this is unlikely. You may experience some soreness after your shoulder injection or after completing some of the exercises suggested by the physiotherapist. This is normal, and you will be given advice on how to manage this soreness.

People sometimes feel uncomfortable answering certain questions about their health. If the researcher, health professional, or follow-up questionnaire asks you questions that you are uncomfortable with, then you do not have to answer them.

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

When is the study starting and how long is it expected to run for? June 2021 to June 2023

Who is funding the study?
National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) programme (UK)
180 Life Sciences (US)

Who is the main contact?
Alison Evans, aff@kennedy.ox.ac.uk
Prof Jagdeep Nanchahal, jagdeep.nanchahal@kennedy.ox.ac.uk

Previous plain English summary:

#### Background and study aims

Frozen shoulder is a common condition affecting approximately 9% of people aged 25-64 years. During the early phase the pain is usually unbearable and the later restriction in movement is severely limiting. It occurs when the flexible tissue (capsule) that surrounds the shoulder joint becomes inflamed, thickened and tight. It's not fully understood why this happens but it is more common in people with diabetes or Dupuytren's disease, which causes the fingers to curl into the palm. It can also occur following shoulder injury or surgery. The pain can be very severe and lasts 3-9 months, followed by a 4-12 month period of increasing stiffness, after which the condition usually improves. Frozen shoulder often affects a person's ability to sleep, carry out everyday activities, and work. Current treatments include rest, painkillers, anti-inflammatories, physiotherapy and steroid injections. If stiffness persists, surgery is sometimes recommended. However, there is no evidence that any of these treatments lead to significant benefit in the long term, with many being ineffective. Steroid injections only help in the short term. The aim of this study is to find out if it is possible to run a larger study to test whether an injection of adalimumab can reduce pain and prevent the disease from getting worse, if given during the early painful phase of frozen shoulder. We need to conduct this smaller study first to be sure it's possible to identify and treat people with early stage frozen shoulder within the current NHS system, before we conduct a much larger study to find out if this treatment works.

#### Who can participate?

In this study we will include adults with painful early stage frozen shoulder who have not yet received treatment.

What does the study involve?

People will be randomised to receive either an injection of the drug adalimumab or a dummy injection of saline (placebo) directly into the shoulder joint, both guided by ultrasound. All participants will also receive standardised advice on how to manage their shoulder pain. We will assess participants before treatment and three months later. Adalimumab has been used very successfully to treat other inflammatory diseases such as rheumatoid arthritis. This drug has been chosen as the biological processes underlying frozen shoulder are similar to those in Dupuytren's disease, where we found it helps to stop the cells causing the disease. The views of patients with frozen shoulder are important to us and have been incorporated into this study. We have worked with a group of patients who have experienced frozen shoulder. All were supportive of our study aims and design. They provided useful feedback that has been incorporated into the study. A patient representative is part of the team for this application. Patient representatives will also be part of the committee that oversees the study.

What are the possible benefits and risks of participating?

We hope the information we obtain from this study will be used to help treat people with frozen shoulder problems more effectively.

There is a possibility you will be harmed by this treatment, although this is unlikely. You may experience some soreness after your shoulder injection or after completing some of the exercises suggested by the physiotherapist. This is normal, and you will be given advice on how to manage this soreness.

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Who is the main contact? Nicola Kenealy, aff@kennedy.ox.ac.uk Prof Jagdeep Nanchahal, jagdeep.nanchahal@kennedy.ox.ac.uk

# Contact information

Type(s)

Public

Contact name

Ms Alison Evans

Contact details

Kennedy Institute of Rheumatology Oxford United Kingdom OX7 7LF +44 (0)1865610612 aff@kennedy.ox.ac.uk

# Type(s)

Scientific

#### Contact name

Prof Jagdeep Nanchahal

#### **ORCID ID**

https://orcid.org/0000-0002-9579-9411

#### Contact details

Kennedy Institute of Rheumatology Oxford United Kingdom OX7 7LD +44 (0)1865612633 jagdeep.nanchahal@kennedy.ox.ac.uk

# Additional identifiers

Clinical Trials Information System (CTIS)

2021-003509-23

Integrated Research Application System (IRAS)

1004069

ClinicalTrials.gov (NCT)

NCT05299242

Protocol serial number

IRAS 1004069, IRAS 50971

# Study information

#### Scientific Title

Anti-TNF (adalimumab) injection for the treatment of adults with frozen shoulder during the pain-predominant phase: a multi-centre, randomised, double blind, parallel group, feasibility study

#### Acronym

Anti-Freaze-F

# Study objectives

To assess the feasibility of conducting a large randomised controlled trial to assess whether an intra-articular injection of adalimumab can reduce pain and improve function in people with pain predominant early stage frozen shoulder

#### Ethics approval required

Old ethics approval format

## Ethics approval(s)

Approved 06/12/2021, North East - Newcastle & North Tyneside 1 Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 2071048285; newcastlenorthtyneside1.rec@hra.nhs.uk), ref: 21/NE/0214

## Study design

Multi-centre randomized double blind parallel group feasibility study

## Primary study design

Interventional

## Study type(s)

**Treatment** 

## Health condition(s) or problem(s) studied

Frozen shoulder

#### **Interventions**

Participants will be randomly allocated (using the OCTRU computer ranomisation system) to receive either: 1) intra-articular injection of anti-TNF (adalimumab 160mg) or 2) placebo injection (saline), both under ultrasound guidance.

A second injection of the allocated treatment (adalimumab 80mg) or equivalent volume of placebo will be administered at 2-3 weeks, unless participants report significant improvement from the first injection and they decline a second injection. All participants will receive a physiotherapy advice leaflet providing education and advice about frozen shoulder and pain management. The total duration of treatment and follow up will be 5 months.

#### Intervention Type

Drug

#### Phase

Phase II/III

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

Adalimumab - Idacio

# Primary outcome(s)

Current primary outcome measure as of 29/03/2022:

- 1. Rate of recruitment of participants with pain predominant frozen shoulder
- 2. Number of participants consenting to be included in the trial.
- 3. Days between baseline assessment and time to first injection
- 4. Days Between first injection and second injection.
- 5. Standard deviation of the Shoulder Pain and Disability Index (SPADI) score and attrition rate at 3 months from baseline in order to estimate the sample size for a definitive trial

Previous primary outcome measure:

Shoulder Pain and Disability will be measured at baseline and 3 months using the SPADI (Shoulder Pain and disability Index).

## Key secondary outcome(s))

Current secondary outcome measures as of 29/03/2022:

- 1. Pain (Shoulder Pain And Disability Index, 5-item subscale) These will be recorded at baseline and 3 months, core range from 0 to 100, lower scores indicate better outcome.
- 2. Function (Shoulder Pain And Disability Index, 8-item subscale) These will be recorded at baseline and 3 months, score range from 0 to 100, lower scores indicate better outcome
- 3. Fear Avoidance Belief Questionnaire score range from 0 to 24, higher scores indicate better outcomes -This will be measured at baseline and 3 months.
- 4. Pain Self Efficacy Questionnaire This will be measured at baseline and 3 months, score range from 0 to 12, higher scores indicate better outcomes
- 5. Insomnia Severity Index This will be measured at baseline and 3 months, Sleep disturbance will be measured using the Insomnia Severity Index, score range from 0 to 28, higher scores indicate worse outcomes.
- 6. Return to desired activities (RDA) These will be recorded at baseline and 3 months, Return to desired activities will be measured using an adapted version of the Disabilities of the Arm, Shoulder and Hand (QUICKDASH) questionnaire.
- 7. Global impression of change These will be recorded at baseline and 3 months, this will be measured using the Likert scale, score range from -5 to +5, higher scores indicate better outcomes.
- 8. Number of visits to Healthcare Professionals These will be recorded at baseline and 3 months.
- 9. Adverse events graded 3 or above (clinician assessed) related to intra-articular injection of adalimumab in the shoulder- These will be recorded after the first injection and at 3 months.

  10. Shoulder range of motion in degrees using a goniometer, These will be recorded at baseline and 3 months.

Previous secondary outcome measures:

- 1. Psychological factors will be measured at baseline and 3 months using the Fear Avoidance Belief Questionnaire
- 2. Pain Self Efficacy Questionnaire will be measured at baseline and 3 months
- 3. Sleep disturbance will be measured at baseline and 3 months using the Insomnia Severity Index
- 4. Return to desired activities will be Patient-reported and reported at baseline and 3 months.
- 5. Global impression of change will be measured at baseline and 3 months using the Likert scale
- 6. Healthcare resource use will be recorded at baseline and 3 months using patient records

#### Completion date

30/06/2023

# Reason abandoned (if study stopped)

Participant recruitment issue

# **Eligibility**

# Key inclusion criteria

- 1. Men and women aged 18 years and above.
- 2. With a new episode of shoulder pain attributable to pain-predominant stage of frozen shoulder (i.e. within approximately 3 months of onset of symptoms) diagnosed using criteria set out in the BESS guidelines
- 3. Who are not being considered for surgery;
- 4. Able to understand spoken and written English;
- 5. Willing and able to give informed consent for trial participation and comply with all study requirements and time line;
- 6. Willing to allow his or her General Practitioner be notified of participation in the trial.
- 7. If female and of child-bearing potential OR if male and their partner is of child-bearing potential willing to use effective contraception throughout the treatment period and for 5 months after the last injection.

#### Participant type(s)

Patient

# Healthy volunteers allowed

No

#### Age group

Adult

# Lower age limit

18 years

#### Sex

All

#### Total final enrolment

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#### Key exclusion criteria

- 1. Those with frozen shoulder secondary to significant shoulder trauma (e.g., dislocation, fracture or full thickness tear requiring surgery) or other causes (e.g. recent breast cancer surgery or radiotherapy);
- 2. Those with a neurological disease affecting the shoulder;
- 3. Those with bilateral concurrent frozen shoulder;
- 4. Those with other shoulder disorders (e.g., inflammatory arthritis, rotator cuff disorders, glenohumeral joint instability) or with red flags consistent with the criteria set out in the BESS quidelines (33):
- 5. Those who have received corticosteroid injection for shoulder pain in the last 12 weeks to either shoulder;
- 6. Those currently taking any anti-TNF drug;
- 7. Those being treated with coumarin anticoagulants, such as warfarin;
- 8. Those who have participated in another research study involving an investigational medicinal product in the past 12 weeks;
- 9. Those with significant renal or hepatic impairment;

- 10. Those with contra-indications to anti-TNF injection:
- 10.1 Known allergy to any anti-TNF agent or any of the excipients;
- 10.2 Known Active tuberculosis (TB) or history of TB.
- 10.3 Known Active infection (chronic or localised) or known history of recurring infections or condition which may predispose patients to infection, including the use of concomitant immunosuppressive medications;
- 10.4 Known Moderate to severe heart failure (NYHA class III/IV);
- 10.5 Those known to have HIV, Hepatitis B or C;
- 10.6 Those at risk of Hepatitis B infection;
- 10.7 Those diagnosed with Multiple Sclerosis (MS) or other central or peripheral nervous system demyelinating disorders;
- 10.8 Those who have ever been diagnosed with cancer, except basal cell carcinoma (BCC);
- 10.9 Those requiring live vaccination prior towithin 12 weeks after of the last trial injection or within the 4 weeks prior to randomisation;
- 10.10 Those taking biologic DMARDS;
- 10.11 Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study

#### Date of first enrolment

31/05/2022

#### Date of final enrolment

07/02/2023

# Locations

#### Countries of recruitment

United Kingdom

England

# Study participating centre

**Good Hope Hospital Treatment Centre**Good Hope Hospital

Rectory Road
Sutton Coldfield
United Kingdom

B75 7RR

# Study participating centre

Sandwell and West Birmingham Hospitals NHS Trust

City Hospital Dudley Road Birmingham United Kingdom B18 7OH

# Study participating centre United Lincolnshire Hospitals NHS Trust

Lincoln County Hospital Greetwell Road Lincoln United Kingdom LN2 5QY

# Study participating centre University Hospital Birmingham

Queen Elizabeth Hospital Edgbaston Birmingham United Kingdom B15 2TH

# Sponsor information

## Organisation

University of Oxford

#### **ROR**

https://ror.org/052gg0110

# Funder(s)

# Funder type

Government

#### **Funder Name**

Research for Patient Benefit Programme

# Alternative Name(s)

NIHR Research for Patient Benefit Programme, Research for Patient Benefit (RfPB), The NIHR Research for Patient Benefit (RfPB), RfPB

# Funding Body Type

Government organisation

# **Funding Body Subtype**

National government

#### Location

**United Kingdom** 

#### Funder Name

180 Life Sciences

# **Results and Publications**

# Individual participant data (IPD) sharing plan

Summary results data will be available on the trial registration database within 12 months of the end of the trial. Requests for data (anonymised participant data) will only be provided at the end of the trial to external researchers who provide a methodologically sound proposal to the trial team aff@kennedy.ox.ac.uk (will be required to sign a data sharing access agreement with the Sponsor) and in accordance with the NIHR guidance. Participant consent for this is included in the informed consent form for the study.

# IPD sharing plan summary

Available on request

# **Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/05/2024	17/05/2024	Yes	No
Protocol article		24/04/2023	09/06/2023	Yes	No
HRA research summary			28/06/2023		No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol (preprint)		12/04/2022	08/06/2022	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes