Anglia Ruskin University | Postgraduate Medical Institute Clinical Trials Unit

**The Feasibility of Fingerprick Autologous Blood (FAB) As a Novel Treatment for Severe Dry Eye Disease (DED): A Randomised Controlled Trial**

| | |
|---|---|
| **Short title/Acronym:** | FAB in DED Trial |
| **Sponsor:** | Bedford Hospital NHS Trust |
| **Representative of the Sponsor:** | Dr Mohammad Wasil<br>Assistant Director, RDI<br>Bedford Hospital NHS Trust<br>Kempston Road<br>Bedford<br>MK42 9DJ |
| **REC reference:** | 17/EE/0508 |
| **IRAS Project ID:** | 233813 |

**Chief Investigator Agreement Page**

The clinical study as detailed within this research protocol **(Version 1.4, dated 10 July 2018)** or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

**Chief Investigator Name:** Mr Anant Sharma

**Chief Investigator Site:** Bedford Hospital NHS Trust

**Signature and Date:**

**Statistician Agreement Page**

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**Statistician Name: Dr Erica Cook**

**Site: University of Bedfordshire, Bedford**

**Signature and Date:**

**Principal Investigator Agreement Page**

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**Principal Investigator Name:**

**Principal Investigator Site:**

**Signature and Date:**

## Study Summary/Synopsis

| | |
|---|---|
| **TITLE** | The Feasibility of Fingerprick Autologous Blood (FAB) as a Novel Treatment for Severe Dry Eye Disease (DED): A Randomised Controlled Trial |
| **SHORT TITLE** | FAB in DED Trial |
| **Protocol Version Number and Date** | **Version 1.4, dated 10 July 2018** |
| **Methodology** | Single-blind randomised controlled Trial |
| **Study Duration** | 24months |
| **Study Centre** | Bedford Hospital NHS Trust, Moorfields Eye Hospital London, |
| **Objectives** | To determine the feasibility of a definitive randomised controlled trial (RCT) to determine effectiveness of the use of fresh autologous blood (FAB) compared to conventional treatment for patients with dry eye syndrome. |
| **Number of Participants** | 60 |
| **Main Inclusion Criteria** | - Patient age > 18 years<br>- Severe symptomatic dry eye disease diagnosed by: Ocular Surface Disease Index (OSDI) score of greater than 33; OR Oxford Corneal Staining grade 2 or greater; OR Schirmer's without anaesthesia <5mm at 5 minutes.<br>- Patient able to consent<br>- Patients able and willing complete the quality of life (QoL) questionnaires required for the study |
| **Statistical Methodology and Analysis** | Data analysis will be primarily descriptive with means, standard deviations and frequency counts calculated for all variables of interest. Exploratory statistical analysis will compare the primary outcome and secondary outcomes between the intervention and control groups at 4 weeks, 8 weeks and 12 weeks (4 weeks post treatment) |

## Glossary of Terms and Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| AR | Adverse Reaction |
| ASR | Annual Safety Report |
| CA | Competent Authority |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| DMC | Data Monitoring Committee |
| EC | European Commission |
| GAfREC | Governance Arrangements for NHS Research Ethics Committees |
| ICF | Informed Consent Form |
| ISRCTN | International Standard Randomised Controlled Trial Number |
| MA | Marketing Authorisation |
| MS | Member State |
| Main REC | Main Research Ethics Committee |
| NHS R&D | National Health Service Research & Development |
| PI | Principle Investigator |
| QA | Quality Assurance |
| QC | Quality Control |
| Participant | An individual who takes part in a clinical trial |
| RCT | Randomised Controlled Trial |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SDV | Source Document Verification |
| SOP | Standard Operating Procedure |
| SSA | Site Specific Assessment |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |

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# 1 Introduction

## 1.1 Background

Dry eye disease (DED) is an umbrella term encompassing a range of diseases estimated to affect 14% of all adults aged 48 to 91. If left untreated, DED can lead to severe reduction in the quality of life of the sufferer. It can also cause loss of vision, pain in response to light, painful recurring stabbing sensations, and the feeling of grit in the affected eye(s). Studies show that moderate to severe DED can be as disruptive as angina (1,2). Despite this, only less than 2% of all UK medical research funding is directed at diseases of the eye, leaving eye research critically underfunded (3).

No curative agents for DED exist. The treatment of the disorder is essentially symptomatic with standard non-surgical treatment focused on the use of artificial tears for lubrication and anti-inflammatory drugs. Anti-inflammatory agents include topical steroids and ciclosporin drops but these can cause side effects that limit their long term use (4). Topical steroids can also cause cataracts and glaucoma, all of which further limit its use. Surgical options for DED include punctal occlusion to reduce tear drainage, punctal cauterization (burning the drainage channel of tears, preventing their outflow) and partial suturing of the eyelids; but these are associated with adverse effects and varying levels of patient tolerability. Overall, available conventional treatment options for DED often only alleviate symptoms, have limited effectiveness, and in most cases patients may fail to respond; although the exact rate of treatment failure is unavailable in the published literature.

The mainstay of non-surgical treatment for DED focuses on the use of artificial tears. These can be purchased over the counter and include brand name products such as Viscotears® and Optrex® (5). Human tears contains an extensive range of growth factors, immunoglobulins, enzymes, cytokines, vitamins and electrolytes and these have been shown in numerous studies to be essential for the maintenance and proliferation of corneal epithelial cells as well as for defence against infection (6). It is well known that artificial tears fails to account for the extraordinarily complex composition of the natural tear film. Also, many artificial tears contain preservatives that have been shown to adversely affect the cornea (7). Crudely, human tears with its vast constituents is essentially filtered blood and as such is an obvious source for a

"tear mimic" containing the substances of tears. Blood, and several blood derived products, including autologous serum, have been studied as tear substitute candidates.

Autologous serum (AS) eye drops have been found in uncontrolled trials to be beneficial in DED patient by improving the ocular surface and reducing symptoms (8–10). However, a Cochrane review concluded that there is inconsistency in evidence on its benefit (11). Obtaining autologous serum requires frequent drawing of blood from the patient— a feature that excludes patients with anaemia or heart failure from using AS. Furthermore it also appears that 100% autologous serum is more beneficial than 50% serum and requires larger volumes of blood and/or more frequent venesection (9). Patients using AS also require access to a fridge as the product needs to be stored at low temperatures; a factor that is likely to be inconvenient for patients. In addition, AS is obtained by processing clotted blood which is often too expensive for the health service to consistently purchase, given the initial cost of £1653.56 and subsequent three-monthly cost of £1131.27 per patient.

The relatively high cost represents the biggest hurdle in the use of AS and is often the reason for delay or inaccessibility in starting treatment for DED using AS. However, we propose that finger prick autologous blood may be a simpler, cost-effective and possibly more acceptable method for treating dry eye disease. For this reason, this study proposes to test the use of finger prick autologous blood (FAB) technique in which whole blood is applied to the eye from a cleaned finger. Autologous fresh blood is already used subconjunctivally to help heal leaking trabeculectomy blebs (12–15). It is also used to help attach limbal autografts in cases of pterygium (16) and vitreoretinal macular hole surgery (17–20), with no adverse effects reported. The FAB method can be used immediately for patients who are awaiting conventional treatment for autologous blood. The objective of this study is therefore to investigate if serum via a drop of fresh blood is an effective treatment for severe dry eye disease which currently require venesected autologous blood and whether this would be particularly useful in the group of patients in whom venesection is contraindicated.

## 1.2 Rationale and Risks/Benefits

This study proposes to test the use of whole, fresh, autologous blood as a treatment for severe dry eye disease. The blood can be obtained from a cleaned finger, pricked by the patient using a diabetic lancet and administered immediately to the dry eye. This allows the delivery of not only most of the aforementioned beneficial components of tears but additional growth factors and proteins, fresh and unprocessed, which can help heal the ocular surface. If validated, this may replace current autologous serum practice and its ease of use, vastly reduced cost with greater convenience may mean that it could be extended to other ocular surface diseases.

The proposing team have completed an exploratory study on the use of finger-prick autologous blood (FAB) for persistent epithelial defects and severe dry eye disease and preliminary results indicate improvement with no adverse events reported (21). The exploratory study included 16 patients with a diagnosis of severe to moderate dry eye syndrome and used the FAB method for treatment. The findings of the study demonstrated mean improvements in visual acuity, Oxford corneal staining grade, tear breakup time, Schirmer's test and dry eye disease questionnaire score. The response rate from participants was good with only a single patient who met the inclusion criteria not wishing to participate in the trial. Both the amount of staining (indicating inflammation and ocular surface damage) and their DED questionnaire scores (indicating severity of their symptoms and impact on quality of life) showed mean improvement which reached statistical significance. A search of clinical databases (Medline, CINAHL and AMED) including on-going trials on the UK CRN portfolio database and related websites (www.controlled-trials.com) did not identified any studies using FAB as a treatment for dry eye disease.

# 2 Trial Objectives and Design

## 2.1 Primary Objective and Endpoints

The primary objective is to determine the feasibility of a definitive randomised controlled trial (RCT) to evaluate effectiveness of the use of fresh autologous blood (FAB) compared to conventional treatment for patients with dry eye syndrome. This will involve specifically assessing the following endpoints:

i. Number of eligible patients within the study population and recruitment time frame.
ii. Percentage of eligible patients accepted for randomisation.
iii. Patient compliance with trial protocol, measured as per self-reported adherence to intervention.
iv. Percentage of patients completing study.

## 2.2 Secondary Objective and Endpoints

The secondary objectives are:

- To determine the effectiveness of the trial intervention and further explore the acceptability of the study design.
- To explore the feasibility of collecting resource use and quality of life data, to inform the design of the health economics component of a future definitive trial.

The secondary end points, which have not been powered for within the feasibility study, include:

| Outcome Measure | Endpoint |
|---|---|
| Reduction in corneal inflammation as indicated by staining on front of the eye | Oxford Corneal Staining Guide |
| Patient pain and symptoms scores | OSDI score |
| Improvement in objective signs of dry eye disease as indicated by visual acuity | Schirmer's test, tear breakup time, lower and/or upper tear menisci height measurement |
| Willingness for patients to be randomised and acceptability of the intervention | Structured qualitative interviews |
| Impact on patients' quality of life | EQ-5D-5L score |
| Cost to the NHS and patient | Use of additional NHS services and privately purchased over the counter treatments related to dry eyes disease |
| Safety measure of pressure within eye | Intra ocular pressure (IOP) score |

## 2.3 Trial Design

Single-blind two-arm feasibility randomised controlled trial of FAB with conventional treatment versus conventional therapy alone for dry eye disease, including a qualitative process evaluation.

- ***Arm A – FAB plus conventional treatment***

The patients will use FAB therapy alongside conventional therapy (artificial tears, ciclosporin drops and punctal plugs/cautery) as recommended by their treating ophthalmologist. A fingertip of the hand will be wiped with an alcohol steret and self-pricked using a standard diabetic lancet. The drop of blood is produced as normal and applied to the lower fornix of the affected eye(s) with the lower lid pulled down slightly by the patient. The blood will be applied four times a day. A fresh finger should be used for each eye. The blood will be wiped away with the alcohol steret. Nails should be kept short and nail varnish should be avoided. FAB should be applied at least 15 minutes after any artificial tears and no drops for at least half an hour afterwards.

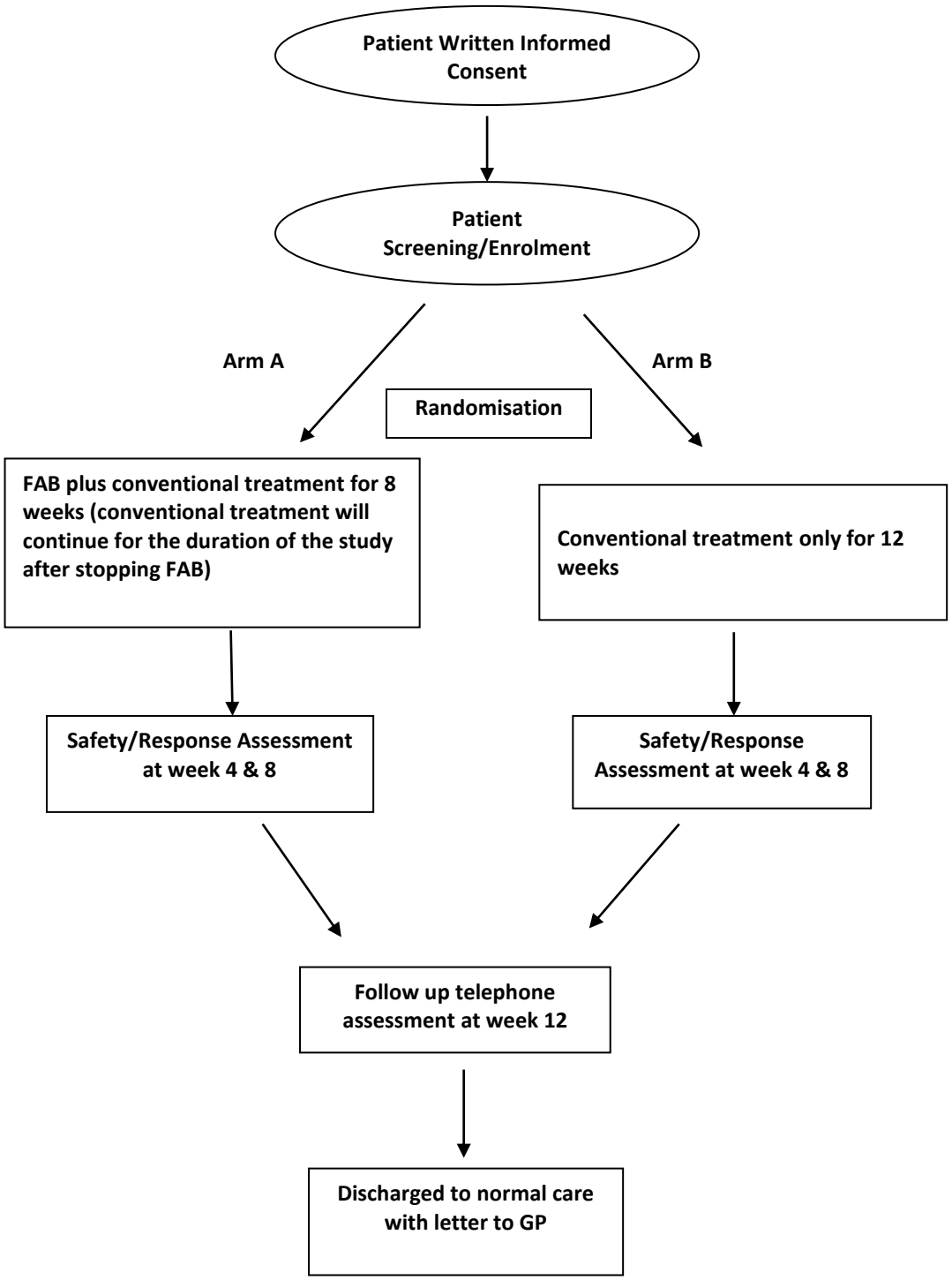
- ***Arm B – Conventional treatment only***

The patients will use conventional therapy (artificial tears, cyclosporin drops and punctal plugs/cautery) as recommended by their treating ophthalmologist.

### 2.3.1 Setting

The study will take place at NHS sites. The main site will be Bedford Hospital NHS Trust and Moorfields Eye Hospital London. Patients will be recruited from corneal and external eye disease clinics at these sites.

## 2.4 Study Scheme Diagram



# 3 Participant Selection

60 patients (30 in each arm) will be recruited into the study. This allows for an attrition rate of 10%.

## 3.1 Inclusion Criteria

i. Patient age ≥ 18 years
ii. Severe symptomatic dry eye disease diagnosed by: Ocular surface disease index (OSDI) score of greater than 33; OR Oxford Corneal Staining grade 2 or greater; OR Schirmer's without anaesthesia <5mm at 5 minutes
iii. Patients on artificial tears and/or lubricating drops/gel four times a day
iv. Patient able to give consent
v. Patients able and willing complete the quality of life (QoL) questionnaires required for the study

## 3.2 Exclusion Criteria

i. Fear of needles
ii. Unable or not willing to carry out repeat finger pricks
iii. Patients with infected finger/s or systemic infection or on systemic antibiotics for infection.
iv. Patients with active ocular infection, active immunological corneal melt, or recurrent corneal erosion.
v. Pregnant or breast feeding women
vi. Previous use of FAB treatment (e.g. from exploratory study)
vii. Systemic illness causing immune system deficiency
viii. Graft versus host disease
ix. Previous use of autologous serum within 3 months
x. Diabetes

# 4 Study Procedures

## 4.1 Informed Consent Procedures

It is the responsibility of the Investigator, or appropriately GCP trained person delegated by the Investigator as documented in the site delegation log, to obtain written informed consent from each participant prior to any participation/study specific procedures. This should follow adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. The participants will be given ample time to consider giving their consent for the study. For this study a minimum of 24 hours will be given during which the consenting team will be contactable over the phone to answer any questions. The date that the Participant Information Sheet (PIS) is given to the participant must be documented within the patient's notes to confirm that sufficient time was given. The Investigator (or other qualified person) will explain to the potential participant that they are free to refuse any involvement within the study or alternatively withdraw their consent at any point during the study and for any reason.

If there is any further safety information which may result in significant changes in the risk/benefit analysis, the PIS and Informed Consent Form (ICF) will be reviewed and updated accordingly. All participants that are actively enrolled on the study will be informed of the updated information and given a revised copy of the PIS/ICF in order to confirm their wish to continue on the study.

## 4.2 Screening Procedures

Patients will have undergone the below procedures as per standard of care which will in turn feed in to the investigator for their review prior to approaching the potential participant.

- Ocular surface disease index (OSDI) score of greater than 33; OR
- Oxford Corneal Staining grade 2 or greater; OR
- Schirmer's without anaesthesia <5mm at 5 minutes

The results of these which will be reviewed by investigator prior to approaching the potential participant.

### 4.3 Randomisation Procedures

Randomisation will be carried out by the Anglia Ruskin Clinical Trials Unit (ARCTU) using the SEALED ENVELOPE randomisation service. SEALED ENVELOPE is a randomisation and online database service developed for clinical trial services. It is an internet based system and will be set for this study by ARCTU in accordance with the protocol. Enrolled patients will undergo 1:1 block randomisation to Arm A or B. The system stores the pre-determined sequence of randomisation and this list is visible to neither the investigator nor ARCTU staff. Once a patient has consented to take part in the trial, they will be randomly allocated to either Arm A to receive FAB and convention therapy or Arm B to receive conventional therapy only. The Research Nurse or Fellow or designated staff will log on to a web browser application and enter the patient's eligibility factors into the system. The treatment allocation will be sent to the research team who will make the necessary arrangements for the patient's treatment plan.

The treating ophthalmologist in clinic will prescribe and counsel all patients on the correct technique for conventional treatment. The unblinded research nurses will provide additional training to the patients on the method of delivering FAB, including the use of a training video. Patients will be advised by the research team to inform their ophthalmologist if they have been started on any new treatment during the trial period by other clinicians or themselves over the counter.

### 4.4 Baseline Procedures

- Patients will undergo the following at baseline:
- Physical examination
- BP and pulse
- Visual acuity test
- Lower and/or upper tear menisci test on optical coherence tomography (OCT, where available)
- Tear breakup time (TBUT)
- Intraocular pressure (IOP)
- Schirmer's test
- Oxford corneal staining grade
- Patient pain and symptom score (OSDI score)
- Lissamine green stain assessment (if available)
- Anterior segment colour photography and cobalt blue fluorescein eye stain photography (if available)
- Anterior segment optical coherence topography (OCT) (if available)
- MMP-9 tear swap (if available)

### 4.5 Schedule of Assessment

| Procedures | Screening (as per standard of care) | Baseline Visit (Day 1) | Week 4 visit (+/- 7days | Week 8 visit (+/- 7days) | Week 12 follow up (Telephone, +/- 7days) |
|---|---|---|---|---|---|
| Informed consent | | x | | | |
| Demographics | | x | | | |
| Medical history | | x | | | |
| Physical examination | | x | x | x | |
| BP and pulse | | x | x | x | |
| Current medical conditions | | x | x | x | |
| Concomitant medications | | x | x | x | |
| Eligibility assessment | x | | | | |
| Randomisation | | x | | | |
| Visit dates and appointment | | x | x | x | |
| FAB treatment (Group A only) | | x | x | x | |
| **Treatment and Follow up Phase** | | | | | |
| Completion of QoL questionnaire (EQ-5D-5L) | | x | x | x | x |
| Completion of Health resource questionnaire | | | x | x | x |
| Review treatment diary | | | x | x | |
| Schirmer's test without anaesthesia (if other criteria not met) | x | x | x | x | |
| Patient pain and symptom score (OSDI score) if other criteria not met | x | x | x | x | x |
| Visual acuity | | x | x | x | |
| Lissamine green stain assessment (if available) | | x | x | x | |
| Anterior segment colour photography and cobalt blue fluorescein eye stain photography (if available) | | x | x | x | |
| Anterior segment optical coherence topography (OCT) (if available) | | x | x | x | |
| MMp-9 tear swap (if available) | | x | | x | |
| Oxford corneal staining grade | x | x | x | x | |
| Lower and/or upper tear menisci height (if available) | | x | x | x | |
| Tear breakup time | | x | x | x | |
| Qualitative interview | | | | x | |

### 4.6 End of Study Definition

The definition of the end of study will be the point where the last patient recruited had the last follow-up visit.

### 4.7 Participant Withdrawal

Patients will be withdrawn from study based on the following:

- New diagnosis of infection on finger or eye
- Requesting to be withdrawn for other reasons such as inconvenience of increased clinic visits
- Pregnancy after recruitment
- Systemic infection, or systemic antimicrobials for infection.
- If finger sore from repeated prick and patient does not want to use another finger.

Any adverse effects will be reported back to the lead investigator at the site and if necessary patients

# 5 Pharmacovigilance

## 5.1 General Definitions

### 5.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with study activities.

### 5.1.2 Serious Adverse Event (SAE)

An SAE fulfils at least one of the following criteria:

- Is fatal – results in death (NOTE: death is an outcome, not an event)
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is otherwise considered medically significant by the Investigator

## 5.2 Investigators Assessment

### 5.2.1 Seriousness

The Chief/Principal Investigator responsible for the care of the participant, or in his absence an authorised medic within the research team, is responsible for assessing whether the event is serious according to the definitions given in section 5.1.

### 5.2.2 Causality

The Investigator must assess the causality of all serious adverse events in relation to the trial treatment according to the definition given

### 5.2.3 Expectedness

The investigator must assess the expectedness of all SAEs according to the definition given. If the SAE is unexpected and related, then it needs immediate reporting.

5.2.4 **Severity**

The Investigator must assess the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on participant/event outcome criteria.

**Mild**: Some discomfort noted but without disruption of daily life
**Moderate**: Discomfort enough to affect/reduce normal activity
**Severe**: Complete inability to perform daily activities and lead a normal life

## 5.3 Notification and reporting Adverse Events or Reactions

If the AE is not defined as SERIOUS, the AE is recorded in the study file and the participant is followed up by the research team. The AE is documented in the participants' medical notes (where appropriate) and the CRF.

## 5.4 Notification and Reporting of Serious Adverse Events

Serious Adverse Event (SAEs) that are considered to be 'related' and 'unexpected' are to be reported to the sponsor within 24 hours of learning of the event and to the Main REC within 15 days in line with the required timeframe. For further guidance on this matter, please refer to Appendix.

## 5.5 Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial participants from any immediate hazard to their health and safety, in accordance with Regulation 30. The measures should be taken immediately. In this instance, the approval of the Licensing Authority Approval prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor and Main Research Ethics Committee (via telephone) of this event **immediately**.

The CI has an obligation to inform both the Main Ethics Committee **in writing within 3 days**, in the form of a substantial amendment. The sponsor must be sent a copy of the

correspondence with regards to this matter. For further guidance on this matter, please refer to Appendix.

### 5.6 Annual Safety Reporting

The CI will send the Annual Progress Report to the main REC using the NRES template (the anniversary date is the date on the MREC "favourable opinion" letter from the MREC) and to the sponsor. Please see appendix for further information.

### 5.7 Overview of the Safety Reporting Process/Pharmacoviligance responsibilities

The CI/PI has the overall pharmacovigilance oversight responsibility. The CI/PI has a duty to ensure that pharmacovigilance monitoring and reporting is conducted in accordance with the sponsor's requirements.

# 6 Statistical Considerations

A detailed data validation will examine completeness, existence and accuracy of collected data to assess data quality and identify missing and conflicting data. To distinguish missing value mechanisms visualisation methods will be used [R package; Visualization and Imputation of Missing (VIM)] (22). Assumptions based on data Missing At Random (MAR)— that is, that a value is missing depends only on observed values and not on unobserved values (23)— will be imputed using multivariate imputations procedures [(R package; Multivariate Imputation by Chained Equations (MICE) (24)]. The statistical analysis will be performed on an intention-to-treat basis and per-protocol and will be reported according to 2010 CONSORT guidelines (25). All statistical analyses will be completed using SPSS Statistics V.22.0 (26). A p-value of <.05 will be accepted as statistical significance.

Conforming to recommendations for feasibility studies, data analysis will be primarily descriptive, with means, standard deviations and frequency counts calculated for all variables of interest. Exploratory efficacy analysis will compare the primary outcome variables derived from the data collected at 8 weeks between the two arms using a marginal general linear model (GLM) with robust standard errors, to allow for clustering by group. Secondary outcomes between the intervention and control groups will be compared at 4 weeks, 8 weeks and 12 weeks (4 weeks post treatment). Safety outcome measures will include IOP rise and any reported infection.

Secondary analyses of the primary outcome, controlling for baseline covariates, will be performed using proportional hazards regression models (27). Analysis of treatment discontinuation adjusted for clinical site, baseline status, and whether the patient is randomized to the FAB or control (conventional treatment only) group will be conducted. Any interaction between baseline status or regimen and treatment will also be assessed. Interactions between significant covariates and treatment effects will be assessed in the context of the proportional hazards models.

### 6.1 Qualitative approach

A nested qualitative approach using in-depth, semi-structured interviews will help us understand the lived experience of people using FAB and factors relating to the ways that clinical departments and healthcare professionals adapt to working with FAB. Topics, questions and probes in the interviews will emerge from three sources: a) the relevant literature; b) our experience of and involvement in clinical ophthalmology; c) consultation with patients. In this feasibility study, we will use a convenience sampling technique for the qualitative work. We will interview all clinicians who administer the intervention in the study and we will aim to interview 10 patients (adjusted for setting, gender and age group representation). Given the resources, we will aim to draw findings from a larger sample in a future study. Interviews will be recorded, transcribed and analysed using the framework analysis. We will structure the analysis of collected data to fit two evaluation frameworks relevant to the successful implementation of FAB:

1) Patient-oriented: Understand the lived experience of patients using FAB with emphasis on intervention acceptability, perceived enablers and barriers for adherence, perceived clarity of advice and guidance and factors relating to the initial uptake of the intervention.

2) Organisation-oriented: Whether and how the use of FAB affected workload and/or workflow; identify process change, adaptation challenges, skills gap; establish treatment fidelity and clinician acceptability.

This phase will work in parallel to the quantitative data collection so that emerging themes can be investigated in later interviews. Even though the feasibility study sample is reasonably limited, we anticipate some useful insights about the use of FAB to occur because of the triangulation between the RCT and the qualitative findings (e.g. reasons for partial adherence).

### 6.2 Economic Evaluation

Good practice recommendations for cost-effectiveness analyses (28) suggest concentrating on the measurement of large cost drivers, with less focus on resources that are not expected to differ between different treatments. Estimation of cost-effectiveness is therefore an iterative

process and by including a health economic component in a feasibility it is possible to consider how the methods might be refined in any future definitive study. In order to estimate costs, informed by previous data collection instruments (Database of Instruments for Resource Use Measurement: http://www.dirum.org/) and NICE guidance (29), a self-report questionnaire will be devised. This will capture the use of NHS services and privately purchased over the counter treatments such as OPTREX. For benefits, the EQ-5D-5L (30) will be used to measure quality of life, enabling QALY (Quality Adjusted Life Year) scores to be calculated. The main purpose of the economic analysis is to inform the decision regarding how and what cost and effect data would be collected within a more definitive study. in order to inform this decision, we will estimate completion rates and seek to identify big cost drivers.

# 7 Data Handling & Record Keeping

## 7.1 Confidentiality

The Investigator has a responsibility to ensure that participant anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. Information with regards to study participants will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

## 7.2 Study Documents

- A signed protocol and any subsequent amendments
- Investigator's Brochure
- Sponsor Self-Monitoring template for the trial team to complete on a regular basis as detailed by the Monitoring section
- Current/Superseded Participant Information Sheets (as applicable)
- Current/Superseded Consent Forms (as applicable)
- Indemnity documentation from sponsor
- Conditions of Sponsorship from sponsor
- Conditional/Final R&D Approval
- Signed site agreement
- Ethics submissions/approvals/correspondence
- CVs of CI and site staff
- Delegation log
- Staff training log
- Site signature log
- Participant identification log
- Screening log
- Enrolment log
- Monitoring visit log
- Protocol training log
- Correspondence relating to the trial
- Communication Plan between the CI/PI and members of the study team
- SAE reporting plan for the study

### 7.3 Case Report Form

Project data collection will be managed by the Clinical Trials Unit Data Manager. The responsibility for data entry rests with the Research Nurse or designated staff who is supported by the Investigator. ARCTU uses an online data management system called MACRO to design and manage eCRFs (Electronic Case Report Forms). ARCTU will work together with the sponsor to design and validate the data collection tools so that they are appropriate for this study. Once a patient is enrolled on the study the research team can access these forms remotely through the Internet portal and study data will be entered and captured for the study. All data will be in anonymised form and patients will be identifiable only by study number. Data will be remotely monitored by ARCTU and discussed at data monitoring committee meetings. Any inconsistencies, validation errors or inaccuracies will be reported to the lead investigator regularly. Once data collection is complete and the data has been validated, a data lock will be performed and analysis will begin.

### 7.4 Record Retention and Archiving

During the course of research, all records are the responsibility of the Chief Investigator and must be kept in secure conditions. When the research trial is complete, it is a requirement of the Research Governance Framework and Trust Policy that the records are kept for a further 20 years.

### 7.5 Compliance

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

## 7.6 Clinical Governance Issues

### 7.6.1 Ethical Considerations

This protocol and any subsequent amendments, along with any accompanying material provided to the participant in addition to any advertising material will be submitted by the Investigator to an Independent Research Ethics Committee. Written Approval from the Committee will be obtained and subsequently submitted to the trusts Research and Development office to obtain Final R&D approval.

## 7.7 Quality Control and Quality Assurance

### 7.7.1 Summary Monitoring Plan

ARCTU will ensure that the project is carried out in accordance with the Research Governance Framework. All research team members will have GCP (Good Clinical Practice) training before the research commences to ensure every aspect from trial design to dissemination is carried out in line with these principals. GCP is an international quality standard that is provided by International Conference on Harmonisation (ICH), an international body that defines standards, which governments can transpose into regulations for clinical trials involving human subjects.

### 7.7.2 Audit and Inspection

**Auditing**: Definition "A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."

The FAB in DED study may receive an audit by any of the methods listed below:

- A project may be identified via the risk assessment process.
- An individual investigator or department may request an audit.
- A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.
- Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.
- Projects may be randomly selected for audit by an external organisation.

Internal audits will be conducted by a sponsor's representative

### 7.8 Non-Compliance

Non-compliance can be defined as 'a noted systematic lack of both the CI and the study staff adhering to SOPs/protocol/ICH-GCP, which leads to prolonged collection of deviations, breaches or suspected fraud.'

These non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which to be escalated. The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependant on the severity. If the actions are not dealt with accordingly, the sponsor will agree an appropriate action, including an on-site audit.

# 8 Trial Committees

### Trial Management Group (TMG)

A Trial Management Group (TMG) has been formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the Data Centres. The TMG will be responsible for the day-to-day running and management of the trial and will meet at least 3 times a year by teleconference.

### Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) has membership from TMG plus independent members, including the chair. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.

### Independent Data Monitoring Committee (IDMC)

The Independent Data Monitoring Committee (IDMC) is the only group who sees the confidential, accumulating data to the trial. Reports to the IDMC will be produced by the trial statistician. The IDMC will meet within 6 months of the trial opening with the frequency of meetings dictated by the IDMC. The IDMC will consider the report for the interim analysis based on the first 30 patients and will decide, keeping in mind the rules described in the statistics section, whether to recommend that the study should continue or be closed. The primary outcome measure for the study addresses toxicity and so it aligns with the IDMC's precautionary role in patient safety. The details of the interim analysis will remain confidential to the IDMC until the study is closed.

# 9 Publication Policy

Data obtained from this study will be published in a suitable peer-review journal and also presented at international ophthalmic conferences including American Academy of Ophthalmology, Royal College of Ophthalmology annual congress, Association for Research and Vision and Ophthalmology, and the European Society of Cataract and Refractive Surgery. Information would be provided to patient groups and charities such as the Sjogren's society and the Royal National Institute of Blind People.

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# Appendix

| | Who | When | How | To Whom |
|---|---|---|---|---|
| **SAE** | Chief Investigator | -Report to Sponsor within 24 hours of learning of the event<br><br>-Report to the MREC within 15 days of learning of the event | SAE Report form for Non-CTIMPs, available from NRES website. | Sponsor and MREC |
| **Urgent Safety Measures** | Chief Investigator | Contact the Sponsor and MREC Immediately<br><br>Within 3 days | By phone<br><br>Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action. | Main REC and Sponsor<br><br>Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt. |
| **Progress Reports** | Chief Investigator | Annually ( starting 12 months after the date of favourable opinion) | Annual Progress Report Form (non-CTIMPs) available from the NRES website | Main REC |
| **Declaration of the conclusion or early termination of the study** | Chief Investigator | Within 90 days (conclusion)<br><br>Within 15 days (early termination)<br>*The end of study should be defined in the protocol* | End of Study Declaration form available from the NRES website | Main REC with a copy to be sent to the sponsor |
| **Summary of final Report** | Chief Investigator | Within one year of conclusion of the Research | No Standard Format<br>However, the following Information should be included:-<br>Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants | Main REC with a copy to be sent to the sponsor |