The ROYAL COLLEGE of OPHTHALMOLOGISTS

Clinical Guidelines

Serum Eye Drops for the Treatment of Severe Ocular Surface Disease

September 2017

Review date: September 2020

The Royal College of Ophthalmologists (RCOphth) is the professional body for eye doctors, who are medically qualified and have undergone or are undergoing specialist training in the treatment and management of eye disease, including surgery. As an independent charity, we pride ourselves on providing impartial and clinically based evidence, putting patient care and safety at the heart of everything we do. Ophthalmologists are at the forefront of eye health services because of their extensive training and experience. The Royal College of Ophthalmologists received its Royal Charter in 1988 and has a membership of over 4,000 consultants of all grades. We are not a regulatory body, but we work collaboratively with government, health and charity organisations to recommend and support improvements in the coordination and management of eye care both nationally and regionally.

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1. Executive Summary

Serum eye drops (SED) are a useful adjunctive treatment for patients with severe ocular surface disease (OSD), especially those with a compromised tear film. Serum contains a large number of epitheliotrophic factors that are present in tears. These factors are likely to be responsible for the therapeutic benefits observed with SED therapy compared to conventional commercially available ocular lubricants. Prescribed and over-the-counter tear substitutes primarily alleviate symptoms through reduction of friction and shear-forces caused by blink-induced biomechanical trauma. This mechanism of action appears largely to be independent of structural chemistry and viscosity of the lubricant product. By contrast, SED provide a variety of nutritional molecules such as vitamins, glucose, growth factors and immunoglobulins. These help to restore an environment that promotes reepithelialisation and supports ocular surface health.

SED are currently classified by the Medicines and Healthcare products Regulatory Agency (MHRA) as an unlicensed medicinal product (i.e. hospital 'special'). The MHRA advises that anyone prescribing an unlicensed product must be satisfied that there is a special need for the unlicensed medicinal product, and that the unlicensed medicine should not be supplied where an equivalent licensed medicinal product can meet the special needs of the patient. This College guideline sets out recommendations and good practice points for the safe use of SED for the treatment of severe OSD. It aims to improve not only compliance with MHRA advice, but also standardise practice and improve patient morbidity. The following areas have been addressed:

- Patient groups that may benefit from the use of SED
- Clinical situations for the use of autologous SED (Auto-SED) and allogeneic SED (Allo-SED)
- SED formulation, frequency of therapy and withdrawal
- Monitoring of treatment efficacy

Full guidance can be found at EYE on line Full report: **www.nature.com/articles/eye2017209**
Executive Summary: **www.nature.com/articles/eye2017208**

Key Recommendations and Good Practice Points for Implementation

The criteria used for the summary of grades of recommendations are found in Table 1 below.

Table 1: Recommendations

Grade	Explanation
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
B	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
C	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
GPP	Good practice points based upon consensual expert opinion where the evidence base does not support A-C grading
MHRA	Medicines and Healthcare products Regulatory Agency Guidance Note 14*
R	Further research is required in this area

** MHRA. 2014. The supply of unlicensed medicinal products ("specials") MHRA Guidance Note 14.*

Recommendation 1: MHRA Guidance Note 14 (2014), supply of unlicensed medicinal products ("specials")	Grade
Serum eye drops are an unlicensed medicine. The MHRA guidance note on the supply of unlicensed medicinal products ("specials") applies to delivery of this service.	MHRA
Note 2.2: Anyone supplying an unlicensed medicinal product, where an equivalent licensed medicinal product is available must be satisfied as to the existence of a special need for the unlicensed medicinal product. MHRA expects that documentary evidence of this special need should be obtained by manufacturers, importers or distributors and that this evidence should be made available on request of the Licensing Authority.	MHRA
Note 2.3: An unlicensed medicine should not be supplied where an equivalent licensed medicinal product can meet the special needs of the patient. Responsibility for deciding whether an individual patient has "special needs" which a licensed product cannot meet should be a matter for the doctor responsible for the patient's care. Examples of "special needs" include an intolerance or allergy to a particular ingredient.	MHRA

Recommendation 2: Serum eye drops should be considered in the following groups of patients	Grade
Patients who have refractory or partially responsive acute or chronic severe ocular surface disease where licensed interventions have been considered.	A
Patients with other ocular surface conditions such as recurrent corneal erosions, persistent epithelial defects and limbal epithelial stem cell failure may benefit if licensed interventions have been unsuccessful.	B
Supportive therapy such as for patients undergoing ocular surface reconstruction.	B

Recommendation 3: Clinical Situations where Autologous versus Allogeneic Serum Eye Drops should be considered	Grade
Autologous Serum Eye Drops (Auto-SED) should be considered for patients who are fit to donate one unit of blood, are able to travel to a blood donor centre, or the patient prefers serum eye drops to be made from their own blood.	GPP
Allogeneic serum eye drops (Allo-SED) should be considered in patients who are unable to donate one unit of blood such as those who are in poor general health, unable to attend a blood donor centre, less than age 16 years, or there is a clinical requirement for urgent treatment.	GPP
Clinical trials comparing the clinical efficacy and cost effectiveness of Auto-SED versus Allo- SED are required.	R

Recommendation 4: Impact of the variability of individual nutritional constituents within the supplied serum eye drops batches on clinical and patient outcomes	Grade
Allo-SED should be considered as an option in patients with uncontrolled diabetes, refractory immune-mediated diseases, those on cytotoxic agents or where their bi- products are known to damage proliferating cells (e.g. cyclophosphamide) and patients with sepsis.	GPP
Detailed serum constituent analyses of sequential donations from patient and healthy donors is required to interrogate bio-variability of each donation and the impact this could have on ocular surface health.	R
Further work on the development of protocols that reduce variability of biological constituents is required e.g. pooling of serum samples from multiple donors with measured ranges of main constituents.	R

Recommendation 5: Concentration of formulation, duration and frequency of SED treatment for patients with ocular surface disease	Grade
Auto-SED and Allo-SED as a 50% dilution in 0.9% Sodium chloride is recommended (as provided by NHSBT, the only accredited SED production facility in the UK).	GPP
Frequency and duration of treatment depends upon individual circumstances. The doctor responsible for patient care should consider withdrawal and stopping strategies in all patients commenced on SED treatment before committing patients to indefinite treatment. Such strategies may include (i) withdrawal of treatment after one year of therapy in patients with ocular surface disease, to define induction of remission before reinstating indefinite treatment if symptoms relapse, or (ii) in patients with persistent corneal epithelial defects, withdrawal of treatment after surface of the eye has healed and restoring treatment if the surface shows signs of breakdown.	GPP
Further research is required on the optimal formulation and diluent. This includes considering whether a 100% formulation is as effective as one that is diluted. A search for vehicles or carriers that improve the retention time and patient satisfaction is recommended.	R
Further work is required on the frequency and duration of serum eye drops treatment used for each clinical indication. Clinical trials should specifically consider when it might be safe to implement treatment withdrawal in patients who have achieved measured success or remission according to pre-set defined criteria.	R

Recommendation 6: Monitoring of treatment response and progression of disease	Grade
Instruments for assessment of the impact of treatment on health-related quality of life and objective grading of patient perceptions of disease using utility instruments specific for ocular surface disease, should be considered for use regularly in the clinical setting. These include the OSDI or the shorter DEQ-5.	GPP
Consistent recording of clinical outcome measures and scoring of disease should be considered. This includes visual acuity, meniscus height, presence of filaments, tear film break-up time, ocular surface staining score e.g. Ocular Staining Score, epithelial defect measurements (if present) and Schirmer's test without anaesthetic.	GPP
It is advised that patients treated with Auto-SED and Allo-SED should be enrolled into a national programme. Frequency and duration of treatment together with serious adverse events should be recorded using a standard reporting procedure. A minimum follow-up of 6 months and then annually should be considered.	GPP
Development and validation of SED-specific patient reported outcome tools and minimal clinical datasets for efficient outcome reporting is required.	R

2. Lay Summary

Ocular Surface Disease (OSD) is a global public-health problem. Severe dryness of the eye has significant impact on a person's physical, emotional and social well-being.

The front of the eye is complex and has an outer surface known as tear film. A range of components contribute to how tears are made, what they contain and how they are distributed to keep the surface of the cornea smooth to enable sight and comfort. Failure of one or more of these complex components due to disease or injury result in dryness of the eye. In its severest form, OSD may lead to blinding complications.

Current Practice for Patients with Ocular Surface Disease

A patient with dry eye disease is treated in a stepped approach. When commercially available artificial tears do not provide relief and the patient does not respond to conventional treatments, the ophthalmologist might suggest that a patient with severe ocular surface disease might benefit from Serum Eye Drops (SED) which are made from blood. Artificial tears made from blood have been shown to be effective because they contain many of the substances found in normal tears. They have been found to be superior to conventional treatment for improving ocular surface health and providing comfort.

Autologous SED (Auto-SED) are made from blood donated by the patient. Patients who are not suitable to provide an autologous donation can receive allogeneic serum drops (Allo-SED) which are made from blood donated by a male volunteer donor. SED are currently reserved for people who have severe disease who have not responded to standard intervention. They are also used for those who require supportive therapy for specialist ocular surgery or for management of ocular surface injury.

The Production of Serum Eye Drops

The NHS Blood and Transplant (NHSBT) has been providing SED since 2003. It is the only accredited production facility in the UK. NHSBT prepares SED from the patient's own blood (Auto-SED) and from individual (not pooled) male-volunteer blood donors (Allo-SED). To make the drops, the donated blood is processed to separate out the serum. Although there are variations in practice in other countries, in the UK, the serum is diluted with 50% saline and is transferred into sterile dropper bottles ready to be frozen. SED have a shelf life in the freezer of 12 months from the date of donation.

The Current Situation and Need for Guidance

Currently, SED is a highly specialised and high cost intervention for patients with Ocular Surface Disease. The Medicines and Healthcare products Regulatory Agency (MHRA), the government body that regulates medicines and medical devices, classifies SED treatment as an unlicensed medicine. This means all licensed medical options should be considered by the doctor responsible for the patient before they are able to prescribe SED. There is geographical inequity in access to treatment that is currently being considered for exclusion from the National Tariff as a High Cost Drug. This guidance aims to set out defined criteria for the use of SED, the monitoring of clinical and patient - reported outcomes and therefore improving patient care and safety whilst on treatment.

Good Practice Points and Recommendations Relevant to Patients

Using The Royal College of Ophthalmologists' Guidelines Development Manual, a systematic review of literature has been carried out in order to focus on the best evidence available so that key questions may be addressed. Recommendations affecting patients as key stakeholders may be summarised as follows.

- SED will benefit patients who have not responded or only partially responded to licensed interventions.
- When comparing the cost and clinical effectiveness of Auto-SED vs. Allo-SED in the treatment of people with OSD, it is recommended that if a patient is unable to donate one unit of blood or a patient requires urgent treatment, Allo-SED are recommended.
- Published studies internationally focus on concentrations of 20%, 50% and 100%. 50% is considered by NHSBT to be the best concentration for general use, although there are no internationally agreed standard procedures for the manufacture.

- There is no clear evidence regarding the duration of treatment or the effect of treatment with SED. It is recommended that treatment should either be for a defined period or there should be an appropriate point when it is stopped in order to assess the outcome. Patient- reported outcomes are an essential tool.

Monitoring

It is recommended that patients treated with Auto-SED and Allo-SED should be enrolled on a national programme of outcome reporting that include patient reported outcomes. Reports should include: frequency and duration of treatment and serious adverse events and reactions. Attempts to withdraw treatment and duration of remission should be recorded.

3. Introduction

3.1 Ocular Surface Disease and the Tear Film

Ocular surface disease (OSD) is a global public-health problem with significant impact on quality-of- life. The ocular surface is a specialised tissue extending from the mucocutaneous junction at the eyelid margin, into the natural gutter (inverse pillar) between the eyelid and eyeball (conjunctival fornix), to the limbus (housing the corneal stem cells) and the cornea (the transparent window in front of the eye). It comprises the surface and glandular epithelia of the cornea, conjunctiva, lacrimal gland, as well as the accessory lacrimal glands, meibomian glands, and their apical (tears) and basal (connective tissue) matrices and eyelids.[1] All components of the system are linked functionally by continuity of the epithelia, their nerve and blood supply together with the endocrine and immune systems. The outer scaffold of the ocular surface, is the apical matrix, known as the tear film. All regions of the ocular surface epithelia produce constituents of the tear film: the corneal and conjunctival epithelia produce hydrophilic mucins that provide a platform for the aqueous component of the tear film; the lacrimal and accessory lacrimal glands secrete water and protective proteins, immunoglobulins, vitamins and nutrients vital for ocular surface health; and the meibomian gland provides the complex superficial tear lipid layer that prevents tear evaporation.[2] These components not only maintain a smooth refractive surface on the cornea to enable sight, the tear film is critical in providing lubrication, physical protection, immunological defence and nutrition to the ocular surface that is regulated by and closely interacts with the neural, endocrine, vascular, and immune systems.

Failure of one or more of these complex components, result in OSD which in its severest form, may lead to blinding complications. These include chronic inflammation, stem cell failure, ulceration, infection, corneal perforation and scarring. Specifically, conditions that lead to alteration in the production, composition, or distribution of the tear film result in symptoms and signs of damage to the structures of the ocular surface.[3] The consequence is noticeable irritation, reduction of visual function, severe sight-threatening complications such as infection and corneal perforation, and importantly, impairment of quality of life similar to that of severe angina, renal dialysis, and disabling hip fracture.[4] A large number of clinical conditions lead to OSD. These conditions include: Sjögren's Syndrome related dry eye, other immune-related dry eye (such as ocular Mucous Membrane Pemphigoid, Stevens-Johnson-Syndrome, Graft Versus Host Disease, and Ulcerative keratitis), neurotrophic cornea, injury (mechanical, chemical, thermal, surgery) and stem cell failure.

3.2 Current Practice

Commercially available artificial tears alleviate biomechanical trauma caused by dry eye disease states, but lack biological properties such as nutrients that promote ocular surface renewal and immunological defence. This is due to difficulty in synthetically replicating the complex nature of the tear-film architecture and chemical composition. Lubricants such as those containing carboxymethylcellulose have improved ocular surface retention and promote epithelial proliferation whereas sodium hyaluronate preparations exploit the property that it is a ubiquitous naturally occurring extracellular matrix glycosaminoglycan found within the ocular tissues. This plays an important role in wound healing, inflammation and lubrication. Attempts to develop a biological tear substitute that has lubricating and nutrient properties promoting ocular surface renewal and immunological defence have been limited. Isolated reports of single compound topical agents such as Vitamin A, epidermal growth factor (EGF) and albumin have shown some in vitro and in vivo efficacy, but clinical response is equivocal and long-term clinical applications have not been developed. Early phase studies are evaluating the use of amniotic membrane extract or constituent eye drops as a potential alternative.

A variety of the sub-categories of treatments have been recommended by the Dry Eye Workshop II and are listed below.[5] It should be noted that the evidence for the various options is heterogenous.

- Environmental and dietary advice
  - Spectacles and Goggles
  - Increase humidity
  - Reduce exposure to air flow/draft and reduce prolonged visual tasks such as computer work, watching television, and reading.
  - Omega 3 fish oils
  - Omega 7
  - Refrain from periocular cosmetics (minimum of 6 weeks trial)

- Lid Care
  - Warm compresses or proprietary lid warming and expressing devices
  - Lid hygiene to reduce lipid biproducts and lipolytic bacteria
  - Treatment of bacterial over-colonisaton
- Non-preserved ocular lubricant eye drops and ointments including
  - Hypromellose
  - Carbomers
  - Hydroxypropylguar
  - High Concentration Hyaluronate
  - Hyaluronate with Xanthangum
  - SoyBean with Phospholipids
  - Ointments
- Lubricants with osmoprotectants
  - Glycerine and L-Carnitine and /or erythritol and/or saccharides
- Lubricants and lipids
  - Hydroxypropyl guar
  - Polar phospholipids
  - Mineral oil, soybean oil with phospholipids
- Alternative non-preserved lubricants
  - Non-preserved saline 0.9%
  - Balanced Salt Solution
  - Tear electrolyte mimetics
- Mucolytics for breakdown of filaments
  - Acetylcysteine preserved
  - Acetylcysteine non-preserved (UL-HOP)
- Topical anti-inflammatory agents
  - Prednisolone non-preserved
  - Dexamethasone non-preserved
  - Topical ciclosporin (ciclosporin 0.2% ointment veterinary preparation, ciclosporin 0.1% (NICE TA269 December 2015)
- Metallomatrix proteinase inhibitors
  - Doxycycline – sub anti-microbial dose
  - Erythromicin
  - Azithromycin
- Punctal occlusion
  - Punctal plugs
  - Punctal cautery
  - Other surgical closure (wounding and suture)
- Secretagogues and Stimulants
  - Oral pilocarpine (aqueous)
  - Oral cevimeline (aqueous – currently not licensed in EU)
  - Topical diquafosol tetrasodium (aqueous and mucin – currently not licensed in EU)
  - Topical Rebamipide ophthalmic suspension (mucin – currently not licensed in EU)
  - Topical testosterone (lipid – currently not licensed in EU)
  - Intranasal neurostimulation (FDA approved)
- Contact lenses
  - Soft contact lenses
  - Rigid gas permeable scleral contact lenses (if Schirmer's I >5mm)
  - Prosthetic replacement of the ocular surface ecosystem (PROSE) or similar scleral contact lens
- Blepharospasm
  - Botulinum Toxin

- 'Topical' Biologics
  - Recombinant human Nerve Growth Factor (rhNGF) 20ug/ml (marketing authorisation European Medicines Agency July 2017) for neurotrophic keratitis may be useful off license, in neural pain and enhancing goblet cell
  - Lymphocyte function–associated antigen-1 antagonist (Lifitegrast) 5% (EU license pending)
  - Interleukin-1 receptor antagonist (IL-1Ra) (Phase II clinical trials)

A guide to tailoring symptoms and signs of dry eye disease stratified according to disease severity level was originally proposed by the Dry Eye Workshop 2007 (Table 2). [6] A staged hierarchy of suggested interventions were refined for each level of severity by the Dry Eye Workshop 2017 (table 3) respectively.[5]

Table 2: Symptoms and signs of dry eye stratified according to disease severity*

Severity Level	1	2	3	4
Discomfort	Mild +/or episodic; occurs under environmental stress	Moderate episodic or chronic; stress or no stress	Severe frequent or constant without stress	Constant, severe and/or disabling
Visual symptoms	None or episodic mild fatigue	Annoying +/or episodic; activity limiting	Annoying, chronic +/ or constant; limiting activity	Constant +/or possibly disabling
Conjunctival hyperaemia	None to mild	None to mild	Mild to moderate	Moderate to marked
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Ocular surface staining	None to mild	Variable	Marked central	Severe punctate erosions
Tear film signs and impact on cornea	None to mild	Mild debris, ↓ meniscus	Filamentary keratitis; mucus clumping; ↑ tear debris	Filamentary keratitis; mucus clumping; ↑ tear debris; ulceration
Lid, Meibomian glands, and ocular surface failure**	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinisation, symblepharon
TFBUT (s)	Variable	≤10	≤5	Immediate
Schirmer's I score (mm/5 min)†	Variable	≤10	≤5	≤2

** adapted from the Dry Eye Workshop 2007[6]*

*** ocular surface failure is defined as failure of mechanisms responsible for maintaining a healthy ocular surface characterised by persistent epithelial defects, keratinisation of the normally non-keratinised ocular surface epithelium, and progressive conjunctival scarring with formation of symblephara (adhesions tethering the tarsal (eyelid) and bulbar (eyeball) conjunctiva).*

†Schirmer's I rates are defined for strips-stimulated tear production performed without the use of topical anaesthetic.

Table 3: TFOS Dry eye workshop II (2017) proposed staged management and treatment recommendations, a, b, c, d*

Step	Treatment
1	***Initiate treatment*** • Education regarding the condition, its management and prognosis • Modification of local environment • Education regarding potential dietary modifications (including oral essential fatty acid supplementation) • Identification and potential modification/ elimination of offending systemic medications and topical medications • Ocular lubricants of various types (if MGD present consider lipid containing supplements) • Lid hygiene and warm compresses of various types
2	***If step 1 options are inadequate, consider:*** • Non-preserved ocular lubricants to minimise preservative-induced toxicity • Tea-tree oil for demodex if present • Tear conservations (punctal occlusion devices, moisture chamber spectacles/goggles) • Overnight treatment with ointments or moisture (such as ointments and moisture chamber devices) • Physician administered, physical heating and expression of the Meibomian glands (including device assisted therapies, such as Lipiflow), and intense pulsed light for Meibomian gland disease • Prescription drugs to manage dry eye disease[d] – Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present) – Topical corticosteroid (limited duration) – Topical secretagogues (if available) – Topical non-glucocorticoid immunomodulatory drugs (such as ciclosporin) – Topical LFA-1 antagonist drugs – Oral macrolide or tetracycline antibiotics
3	***If step 2 options are inadequate, consider:*** • Oral secretagogues • **Autologous and allogeneic serum eye drops** • Therapeutic contact lens options (soft bandage contact lenses, rigid scleral contact lenses)
4	***If level 3 options are inadequate, consider:*** • Topical corticosteroid for longer duration (Tip: RNFL of the optic disc and visual fields) • Amniotic membrane grafts • Surgical punctal occlusion • Other surgical approaches e.g. tarsorrhaphy, salivary gland transplantation

** reproduced and adapted from The Ocular Surface Journal, Dry Eye Workshop II (2017).[5]*

a. Potential variations within the disease spectrum are acknowledged to exist between patients and the management options listed above are not intended to be exclusive. The severity and aetiology of the DED state will dictate the range and number of management options selected from one or more steps.

b. One or more options concurrently within each category can be considered within that step of the dry eye disease state. Options within a category are not ranked according to importance and may be equally valid.

c. It should be noted that the evidence available to support the various management options differs and will inevitably be lower for newer management options. Thus, each treatment option should be considered in accordance with the level of evidence available at the time management is instigated.

d. The use of prescription drugs needs to be considered in the context of the individual patient presentation, and the relative level of evidence supporting their use for that specific indication, as this group of agents differs widely in mechanism of action.

3.3 Serum Eye Drops

3.3.1 Physiology

Serum eye drops (SED) are an adjunctive treatment for complex, often immune-mediated, OSD where the production and quality of the tear-film has been compromised leading to debilitating symptoms and severe sight-threatening damage of the surface of the eye; or as supportive therapy for surgical procedures or acute injury (chemical, thermal, immunological). Serum contains a large number of epitheliotrophic factors that are present in tears and are likely to be responsible for the therapeutic effects observed in patients with OSD over and above conventional commercially available lubricants.[2,3] SED provide the only nutritional tear film substitute available in the United Kingdom that possesses biological properties to help provide an ocular surface environment that promotes epithelial cell renewal and restore homeostasis. This is due to the similarities between the constituents of and the natural (whole) tear film as shown in Table 4.

Table 4: Similarities of key constituents in whole tears and serum (reproduced from Rauz and Saw)7

Parameter	Whole Tears	Serum
pH	7.4	7.4
Osmolality	298	296
EGF (ng/ml)	0.2-3.0	0.5
TGF-β(ng/ml)	2-10	6-33
NGF (pg/ml)	468.3	54.0
IGF (ng/ml)	0.31	105
PDGF (ng/ml)	1.33	15.4
Albumin (mg/ml)	0.023	53
Substance P (pg/ml)	157	70.9
Vitamin A (mg/ml)	0.02	46
Lysozyme (mg/ml)	1.4	6
Surface IgA (µg/ml)	1190	2
Fibronectin (µg/ml)	21	205
Lactoferrin (ng/ml)	1,650	266

Since the first reported use of auto-SED by Fox in 1984,[8] SED have demonstrated to be effective for the treatment of complex dry eye disease secondary to a wide range of clinical conditions causing ocular surface disease (Stevens-Johnson syndrome, Sjögren's syndrome, persistent epithelial defects, graft-versus-host disease, post-LASIK dry eyes, neurotrophic keratopathy, diabetes mellitus, superior limbic keratoconjunctivitis, recurrent corneal erosions, aniridic limbal stem cell deficiency) and supportive therapy for ocular surface reconstruction and stem cell therapy. Demand for the service has been steadily increasing but access to care has been restricted due to a number of multifactorial reasons including licensing status and cost. Finger-prick autologous

blood is occasionally used as a cheaper alternative.[9] The SED treatment is reserved for patients who have severe disease that is refractory to standard interventions, or for those who require supportive therapy for specialised ocular surface surgical procedures, or for use in the acute management of ocular surface injury (chemical, mechanical, thermal, immunological).

3.3.2 Serum Eye Drops Service UK

NHS Blood and Transplant (NHSBT) has been providing a SED service since 2003 following the publication from Noble et al.[10] and prepares SED from the patient's own blood (Auto-SED) and more recently from 2014, from individual (not pooled) male-volunteer blood donors (Allo-SED). SED is an unlicensed medicine that is currently being considered for exclusion from the National Tariff as a High Cost Drug. NHSBT follows strict standard operating procedures. Patients for Auto-SED are required to be of reasonably good health, with no significant cardiovascular or cerebrovascular disease, and free of bacterial infection. Anaemia (Hb <11 g/dl) is a relative contraindication. Allo-SED can be provided for patients who are medically unsuitable to provide an autologous donation.

Donations are screened as for hepatitis B and C, HIV I & II, HTLV I & II and syphilis. One full blood donation produces up to 150 bottles of SED bottles diluted 50% with saline with a shelf life of 12 months from the date of donation. The majority of the early literature focuses on Auto-SED with recent emergence of interest in Allo-SED. Allo-SED has the advantage of providing treatment if the requirement is immediate or if the patient is unable to donate blood due to their complex medical history (immune-mediated disease, blood cancers, intensive care patients), poor cardiovascular status, anaemia and poor venous access. The current patient population eligible for treatment are those with OSD refractory to conventional licensed therapy, those requiring acute management of ocular surface injury and supportive therapy for ocular surface reconstructive procedures.

3.3.3 Outcome measures

Putative data collection tools for baseline and follow-up for both clinical and patient-reported outcomes (ocular surface disease index (OSDI)) with visual analogue scale, have been used by NHSBT. Interim data analyses (July 2017) of the OSDI score shows a median reduction in OSDI score of 56.7%, from 57.7 (severe; Q1-Q3 range, 40.6-82.5) pre-commencement of treatment to 25 (moderate; Q1-Q3 range, 12.3-48.6) after 4 months of treatment. Significant improvements are observed in both Allo-SED and Auto-SED groups (Figure 1) and no difference in patient benefit was observed between Allo-SED and Auto-SED.

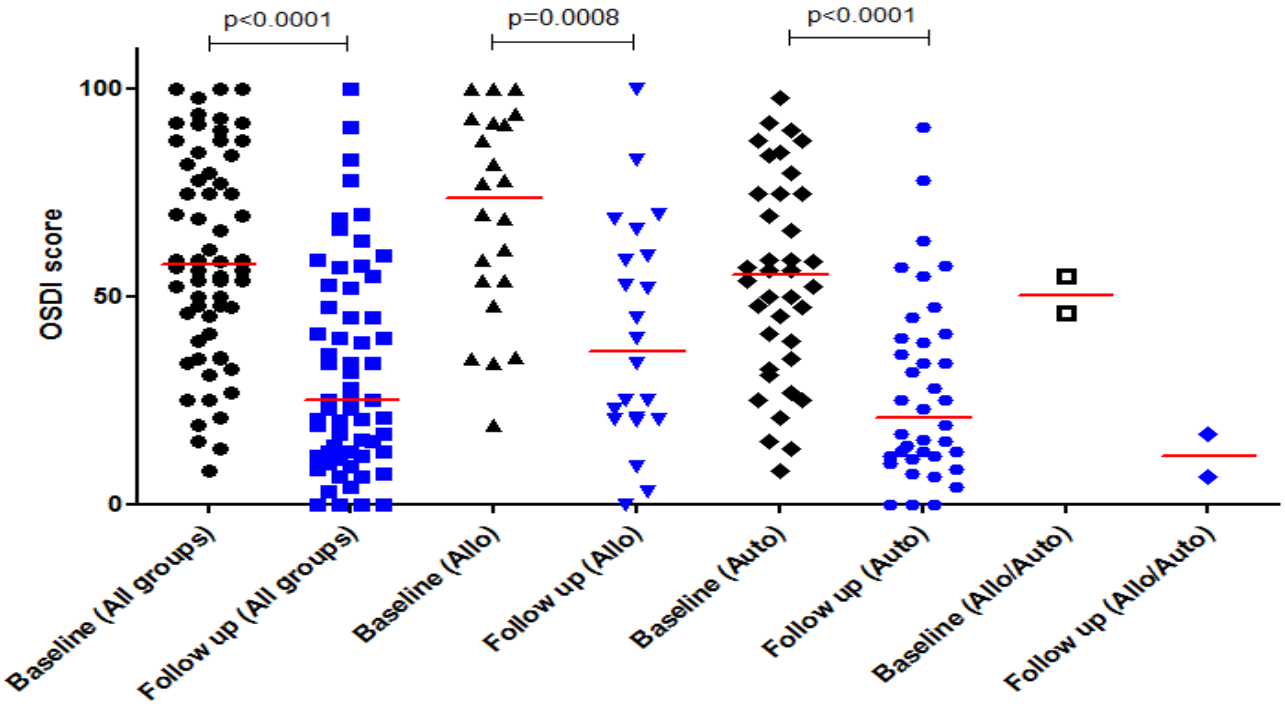

Figure 1: ***Impact of SED therapy on the ocular surface disease index (OSDI) score.*** (All patients, n=62; Allo, n=22; Auto, n=38; Allo/Auto (patients initiated on Allo-SED for speed then switched to Auto-SED), 2; p values derived from Wilcoxon matched-pairs signed rank test).

3.4 Population to whom the Guideline applies e.g. the age range, gender, clinical description (ICD10) and co-morbidity (ICD10) and any exclusions

The provision of SED is applicable to any patient with ocular surface disease. Children <16 years of age are provided with non-CJD risk allogeneic serum imported from Europe. Auto-SED is contraindicated in patients who are anaemic, have insufficient venous access, unable to donate the full unit of blood, unable to give consent, and are unconscious or unable to travel to a donor centre. Allo-SED has the advantage of providing treatment if the requirement is immediate or if the patient is unable to donate blood due to their complex medical history (immune-mediated disease, blood cancers, and critical care patients), poor cardiovascular status, anaemia and poor venous access. A diagnostic breakdown of the population who could potentially benefit from SED is given in Table 5.

*Table 5: Examples of the patient populations who may benefit from SED therapy**

Main category	Examples
Primary and secondary Sjögren's Syndrome	
Other immune related ocular surface disease	Ocular Mucous Membrane Pemphigoid Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis Graft-versus-Host Disease Other immune-related ocular surface disease
Non-immune ocular surface disease	
Neurotrophic disease	Diabetic cornea Herpetic aetiology Other neuropathic disease including secondary to non-ocular, extra-ocular and neuro surgery etc.
Injury	Ocular Surface Toxicity Chemical Thermal Mechanical Radiation Surgical Other Injury
Supportive	Ocular surface reconstruction Corneal transplantation Other supportive e.g. critical care unit/high dependency/burns unit
Inherited ocular surface disease	Aniridia Ectodermal dysplasia Epidermolysis Bullosa Other inherited ocular disease

* *This is not a comprehensive list. Examples are given for guidance only*

3.5 Scope for Change

SED is a highly specialised, high cost intervention currently classified by the Medicines and Healthcare products Regulatory Agency (MHRA) as an unlicensed medicine. It is reserved for patients with ocular surface or corneal conditions including severe anterior segment inflammation refractory to conventional topical therapy[11] and other equivalent licensed options. There are no nationally accredited criteria for entering the SED programme and there is an absence of robust systems for recording of outcomes or for implementing withdrawal/stopping strategies. This has led to variation in practice and geographical inequity in access to treatment.

4. Objectives

4.1 Aims

Serum eye drops are an unlicensed medicinal product. These Guidelines aim to provide evidence-based recommendations and good practice points for the safe use of SED for the treatment of severe ocular surface disease. They will set out criteria outlining when SED should be considered and provide guidance on how to document outcomes. Standardising enrolment and clinical documentation will ultimately improve patient safety and care.

4.2 The clinical questions covered by the guidelines

Q1. Are SED more effective at treating patients with ocular surface disease than conventional treatment?

Q2. Is there evidence of superiority in the cost and clinical effectiveness of autologous serum eye drops (Auto-SED) versus allogeneic serum eye drops (Allo-SED) at treating patients with ocular surface disease?

Q3. What effect does dose size have on the effect of treatment with SED for patients with ocular surface disease?

Q4. What effect does concentration of formulation have on the effect of treatment with SED for patients with ocular surface disease?

Q5. What effect does duration of treatment have on the effect of treatment with SED for patients with ocular surface disease?

Q6. What effect does frequency of treatment have on the effect of treatment with SED for patients with ocular surface disease?

Q7. Which clinical outcome measures best record the treatment effect for monitoring ocular surface disease?

Q8. Which patient reported outcome measures best record the treatment effect for monitoring impact on patient debility?

4.3 Description of the key stakeholders and end users

4.3.1 Target Audience:

- Ophthalmologists (Consultants and Specialty & Associate Specialist (SAS) doctors) caring for adults and children with OSD in secondary and tertiary care.

4.3.2 Other Beneficiaries:

- Multi-professional teams who have patients with ocular surface manifestations of systemic diseases including Haematologists, Rheumatologists, Neurologists, Dermatologists, General Physicians and General Practitioners who will review patients with ocular surface disease.
- Healthcare professionals and practitioners such as those working in Intensive Care Medicine, specialist Nurses, Optometrists and Orthoptists.
- The guideline should also be of relevance to Specialist Trainees and Specialist Nurses.
- Commissioners and providers of services for adults and children with OSD.
- Adults and children with ocular surface diseases and their families and carers.

4.3.3 Stakeholders:

- The Royal College of Ophthalmologists
- The Bowman Club
- NHS Blood and Transplant (NHSBT)

- Ocular Tissue Advisory Group (OTAG)
- Serum Eye Drops Patient Support Group
- British Society of Blood and Marrow Transplant (BSBMT)
- British Society of Rheumatology
- British Sjögren's Syndrome Association

5. Methods

5.1 Methodology

This guideline has been developed in accordance with the Guideline Development Manual of The Royal College of Ophthalmologists (found at RCOphth.ac.uk) following the pre-specified stages to ensure that the recommendations are aligned with the strength of evidence available from the review of the literature.

5.2 Search strategy

Key questions for the guideline were developed using the Patient, Intervention, Comparison and Outcome (PICO) framework to provide a structured basis for identifying the evidence. A systematic review of the literature was undertaken using the explicit search strategies devised in collaboration with the Cochrane Eyes and Vision Group. Databases searched include Medline, Embase, and the Cochrane Library for literature published between 1992 and 2017. Further searches were undertaken on various websites including the US National Guidelines Clearinghouse. All PICO search strategies used are shown in **Appendix 1.**

The evidence base for this guideline was identified and synthesised in accordance with the accepted methodology with each of the selected papers was evaluated by two members of the group using standard checklists before conclusions were considered as acceptable evidence. The literature search focused on the best available evidence to address the key review questions by including the following types of evidence:

- Published guidelines
- Systematic reviews
- Randomised controlled trials
- Cohort and case control studies
- Case series

Papers not published in the English language, abstracts and letters were excluded.

5.3 Levels of Evidence and Grades of Recommendations

Evidence was graded by the Guideline Development Group according to its strength using the Scottish Intercollegiate Guidelines Network framework (SIGN 50 – Table 6). The strength of each recommendation took into account the quality of the evidence.

Table 6: Scottish Intercollegiate Guidelines Network framework (SIGN 50)

Type of Evidence	Description
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal

Type of Evidence	Description
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus

Using the evidence identified the Guideline Development Group determined the guideline recommendations. The strength of each recommendation has been based upon the quality of the evidence and the potential for patient benefit.

This guideline makes a **strong** recommendation where:

- The evidence is of high quality
- Estimates of the effect of an intervention are precise (i.e. there is a high degree of certainty that effects will be achieved in practice)
- There are few downsides of therapy
- There is a high degree of acceptance among patients

And a **conditional** recommendation is made where:

- There are weaknesses in the evidence base
- There is a degree of doubt about the size of the effect that can be expected in practice
- There is a need to balance the upsides and downsides of therapy
- There are likely to be varying degrees of acceptance among patients

The strength of the recommendation has been graded by the Guideline Development Group using the methodology from the Scottish Intercollegiate Guidelines Network (SIGN 50). The grade of recommendation relates to the strength of the evidence on which the recommendation is based (Table 7). It does not reflect the clinical importance of the recommendation.

Table 7: Grade of recommendation

Grade	Explanation
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
B	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
C	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
GPP	Good practice points based upon consensual expert opinion where the evidence base does not support A-C grading
MHRA	Medicines and Healthcare products Regulatory Agency Guidance Note 14
R	Further research is required in this area

6. Results

6.1 Q1. Are SED more effective at treating patients with ocular surface disease, than conventional treatment?

6.1.1 Scope:

There is wide consensus amongst specialists in ocular surface disease that SED have a role in the treatment of disorders such as severe immune-mediated dry eye disease, persistent and recurrent corneal epithelial defect, neurotrophic keratopathy and patients who require supportive therapy post ocular surface reconstruction. The treatment is reserved for those who are unresponsive or partially responsive to available licensed conventional therapeutic options considered to be appropriate for the patient. The evidence underpinning the benefit of treating patients with ocular surface disease and whether SEDs are more effective than those on conventional treatment was reviewed.

6.1.2 Evidence:

A Cochrane review on the use of SED in adults with dry eye was published in 2017[12] and summarised the results of 5 RCTs (Celebi 2014;[13] Kojima 2005;[14] Noda-Tsuruya 2006;[15] Tananuvat 2001;[16] Urzua 2012[17]). They concluded that SED 20% may provide some benefit in improving patient-reported symptoms in the short term (2 weeks), but that there appears to be no evidence of improvement over a longer period. Of note, there was unclear evidence to suggest improvement for objective measures of the ocular surface disease. The authors recommended that further large, high-quality RCTs using standardised questionnaires, objective clinical tests and objective biomarkers are warranted to assess the benefit of SED in the longer term. (Evidence 1++, Positive/Equivocal).

Another systematic review[18] evaluated the use of blood derived topical therapy (including SED) in ocular surface disease, concluding that the use of SED in dry eye disease improved OSDI scores, fluorescein staining score and TBUT, as well as reducing concurrent use of topical lubricants. SED also appeared to be effective in the treatment of PED, but study numbers were small. (Evidence 1++, Positive/Equivocal).

Whilst there is paucity of strong supporting evidence, several reviews have reported a trend for superiority of SED in alleviating some of the clinical signs and symptoms in Sjögren's[19] and non- Sjögren's dry eye disease, limbal epithelial stem cell deficiency, graft-versus-host-disease, persistent epithelial defects, recurrent corneal erosions, post-refractive surgery[20] and Stevens-Johnsons syndrome/toxic epidermal necrolysis.[21] A double masked RCT in 40 eyes[22] demonstrated improved tear film stability and patient comfort with SED, supported by three other case series in 123 eyes of 63 dry eye patients[23], 56 eyes of 28 patients[24] and in 17 patients with Graft Versus Host Disease[25]. In another RCT, Improved recovery time from corneal abrasions induced during vitrectomy surgery has also been shown.[26]

A publication by a panel of North American experts on the management of dry eye in Sjögren's syndrome[27] corroborated the recommendation for the use of serum drops by the 2007 International Management and Therapy Subcommittee of the International Dry Eye Workshop I and II.[5] [6] These publications acknowledged the limited evidence available, but recommended use of SED for severe dry eye unresponsive to conventional measures.

Table 7 shows a summary of all the studies included in the evidence review.

In the United Kingdom, the NHSBT is conducting an evaluation of new patients who are enrolled onto the SED programme. These data, capture baseline and follow up findings at 4 months. Data being collected include patient perceptions of their disease using a validated tool (ocular surface disease index (OSDI)) and clinical findings using a corneal function score (Oxford Ocular Surface Grading System) together with tear film break-up time and Schirmer's test without anaesthetic, both performed using DEWS 2007 methodology. The results are pending but these should provide useful information on the effectiveness of SED amongst patients with ocular surface disease and will form the largest published case series using Auto-SED and Allo-SED.

6.1.3 Recommendation:

SEDs will benefit:

1. Patients who have refractory or partially responsive acute or chronic severe ocular surface disease where licensed interventions have been considered (Recommendation grade A)
2. Patients with other ocular surface conditions such as recurrent corneal erosions, persistent epithelial defects and limbal epithelial stem cell failure may benefit if licensed interventions have been unsuccessful (Recommendation grade B)
3. Patients who require supportive therapy such as for patients undergoing ocular surface reconstruction (Recommendation grade B)

6.2 Q2. Is there evidence of superiority in the cost and clinical effectiveness of autologous serum eye drops (Auto-SED) versus allogeneic serum eye drops (Allo-SED) at treating patients with ocular surface disease?

6.2.1 Scope:

Patients with inflammatory ocular surface disease frequently have systemic manifestations which preclude the ability to donate blood for the production of autologous serum, require Allo-SED. This may be due to general health issues such as patients who have poor venous access and patients who are unable to attend an apheresis/donor centre. Such patients include those patients with poor mobility e.g. multiple sclerosis, rheumatic disease and those in critical care situations.

The evidence interrogating efficacy, superiority and cost-benefit of Allo-SED versus Auto-SED in these situations was evaluated.

6.2.2 Evidence:

There are no studies that have performed a direct comparison of effectiveness of Auto-SED versus Allo-SED in the treatment of ocular surface disease. Lekahnont et al.[28] performed a prospective study of 181 eyes, where 178 were received Auto-SED, and 3 Allo-SED. Given however, the large discrepancy in group sizes, this was not felt to be a valid comparison study.

There are also no published studies comparing the direct and indirect cost effectiveness of Auto-SED versus Allo-SED, or studies that determine the impact of the economic benefit or burden of the treatment. In the United Kingdom, the NHSBT provides Auto-SED and Allo-SED at a cost of approximately £1,100 for 3-5 months' supply (including delivery to the patient's home address with same day courier).

6.2.3 Recommendation:

1. Autologous Serum Eye Drops (Auto-SED) should be considered for patients who are fit to donate one unit of blood, are able to travel to a blood donor centre, or the patient prefers serum eye drops to be made from their own blood (Recommendation grade GPP)
2. Allogeneic serum eye drops (Allo-SED) should be considered in patients who are unable to donate one unit of blood such as those who are in poor general health, unable to attend a blood donor centre, less than age 16 years, or there is a clinical requirement for urgent treatment (Recommendation grade GPP)
3. Clinical trials comparing the clinical efficacy and cost effectiveness of Auto-SED versus Allo- SED are required (Recommendation grade R)

6.3 Q3. What effect does dose size have on the effect of treatment with SED for patients with ocular surface disease?

6.3.1 Scope:

SED provide a physiological tear substitute for patients with ocular surface disease with nutritional properties in addition to reduction of biomechanical trauma or friction provided by commercially available substitutes. Published comparisons of serum, plasma and tear components highlight similarities between these biofluids but do not provide ranges to gauge the bio-variability of each constituent within Auto-SED versus the natural tear film. The composition of the Auto-SEDs made from donations from patients with diabetes, immune-mediated

diseases, those on cytotoxic drugs or with sepsis will have potentially harmful serum constituents that could lead to severe ocular surface toxicity. Patients with underlying immune-mediated disease may have circulating antibodies, growth factors and pro-inflammatory cytokines within their serum that theoretically may exacerbate disease if administered topically to the surface of the eye. These patients may benefit from Allo-SED rather than Auto-SED. Patients in this grouping include those with graft-versus-host disease, acute toxic epidermal necrolysis or mucous membrane pemphigoid.

The evidence regarding the biological variability of the composition of Auto-/Allo-SED and the dose of each blood constituent that is optimal for a therapeutic effect, versus the dose that could lead to ocular surface toxicity, was considered to be important. The literature in this area was reviewed.

6.3.2 Evidence:

There are no published clinical trials that specifically compare the effects of individual constituents in SED for the treatment of ocular surface disease. This includes serum levels of putative toxins, although studies evaluating the pathophysiology of various OSDs highlight systemic activation of the adaptive immune response and subsequent expression of proinflammatory mediators at the ocular surface.[3]

6.3.3 Recommendation:

1. Allo-SED should be considered as an option in patients with uncontrolled diabetes, refractory immune-mediated diseases, those on cytotoxic agents or where their bi-products are known to damage proliferating cells (e.g. cyclophosphamide) and patients with sepsis. (Recommendation grade GPP)
2. Detailed serum constituent analyses of sequential donations from patient and healthy donors is required to interrogate bio-variability of each donation and the impact this could have on ocular surface health (Recommendation grade R)
3. Further work on the development of protocols that reduce variability of biological constituents is required e.g. pooling of serum samples from multiple donors with measured ranges of main constituents. (Recommendation grade R)

6.4 Q4. What effect does concentration of formulation have on the effect of treatment with SED for patients with ocular surface disease?

6.4.1 Scope:

Published data shows the similarities between tear and serum constituents. Manufacturing process (clotting time, centrifuging, temperature etc) varies from country to country and there appears to be no internationally agreed standard operating procedures for the production of SED.[29] This includes whether it is clinically more effective to treat patients with SED manufactured without dilution and delivered as 100% serum, or if diluted, what is the optimal diluent or carrier and concentration to achieve the desired clinical effect.

6.4.2 Evidence:

Published studies have used varying concentrations of SED: most commonly 20%, followed by 50% and 100% (Table 8). SEDs are usually diluted with Sodium Chloride 0.9% to achieve the desired final product concentration.

There is only one published study (Cho et al 2013)[30] which compared the efficacy of SED with different diluents in patients with dry eyes (Sjögren's syndrome and non-Sjögren's syndrome) and persistent epithelial defects. In this study, SED were administered as: 100% serum, 50% serum with 0.9% NaCl, 50% serum with sodium hyaluronate 0.3% or 50% serum with ceftazidime 5%. The authors concluded that 100% SED helped to improve subjective symptoms and objective findings in both Sjögren's and non-Sjögren's dry eye, and increases healing speed in eyes with persistent epithelial defects. However, in the non-Sjögren's dry eye group, 50% SED (diluted with 0.9% NaCl) showed similar improvements as 100% SED. The authors also reported that SED diluted in 0.9% NaCl showed the best effects, and despite their expectations, there was no synergistic effect of hyaluronic acid when used at a diluent for SED. SED diluted with ceftazidime was found to be least effective due to the antibiotics own epithelial toxicity. The results of this study are summarised in Table 9.

6.4.3 Recommendation:

1. The use of Auto-SED and Allo-SED as a 50% dilution in 0.9% Sodium chloride is recommended (as provided by NHSBT, the only accredited SED production facility in the UK) (Recommendation grade: GPP)

6.5 What effect does duration (Question 5) and frequency (Question 6) of treatment have on the effect of treatment with SED for patients with ocular surface disease?

6.5.1 Scope:

Clinical guidance given to patients on how frequently they should administer SED and for what duration varies from patient to patient, and their underlying clinical condition. Some patients commence treatment for a short duration (1-2 donations providing 4-6 months treatment) on a 2 hourly basis to determine whether a high pulse of topical treatment may induce remission whilst others are on life-long treatment. The evidence for optimal duration and frequency, and indication for when to stop treatment was considered to be important.

6.5.2 Evidence:

No studies have examined optimal frequency and/or duration of SED therapy for a specific clinical indication. There are no studies evaluating when it might be safe to stop SED therapy.

There are considerable variations in treatment frequency in published studies (Table 8 and Table 9: 4x/day to hourly usage). There is no clear evidence to suggest that more frequent instillation results in improved subjective symptoms and objective clinical findings. Similarly, the optimal duration of treatment with SED is unclear due to heterogeneity in the published studies. The duration of treatment in studies ranges from 2 weeks to 6 months – this however often coincides with the study duration, and it is unclear how many patients continue on SED after conclusion of the study.

6.5.3 Recommendation:

1. Frequency and duration of treatment depends upon individual circumstances. The doctor responsible for patient care should consider withdrawal and stopping strategies in all patients commenced on SED treatment before committing patients to indefinite treatment. Such strategies may include (i) withdrawal of treatment after one year of therapy in patients with ocular surface disease, to define induction of remission before reinstating indefinite treatment if symptoms relapse, or (ii) in patients with persistent corneal epithelial defects, withdrawal of treatment after surface of the eye has healed and restoring treatment if the surface shows signs of breakdown. (Recommendation grade GPP)
2. Further research is required on the optimal formulation and diluent. This includes considering whether a 100% formulation is as effective as one that is diluted. A search forvehicles or carriers that improve the retention time and patient satisfaction is recommended. (Recommendation grade R)
3. Further work is required on the frequency and duration of serum eye drops treatment used for each clinical indication. Clinical trials should specifically consider when it might be safe to implement treatment withdrawal in patients who have achieved measured success or remission according to pre-set defined criteria. (Recommendation grade R)

6.6 Which clinical (Question 7) outcome or patient reported (Question 8) outcome measures best record the treatment effect for monitoring ocular surface disease and the impact on patient debility?

6.6.1 Scope:

Consistent recording of clinical and patient reported outcomes enables a unified approach to objective assessment of treatment response to novel or highly specialised interventions such as SEDs. The generation of cohort registries and datasets (as recommended by the Quality, Innovation, Productivity and Prevention programme) facilitates the quantification of efficacy in a clinical setting, serious adverse events, and ultimately the impact of SED on the health economic burden.

Nevertheless, it is recognised that patient perceptions of disease influencing severity scoring outweigh observed clinical signs in some patients with ocular neuropathic pain. The presence and validity of published clinical and patient reported outcome instruments for use in monitoring the clinical effect of SED for standardisation of outcome reporting and patient benefits, was determined.

6.6.2 Evidence:

There is a heterogeneity in outcome reporting in the monitoring of the effects of SED. There are no studies that have specifically validated objective scores for clinical examination findings (ocular surface staining score, Schirmer's test, tear film break-up time), laboratory investigations (impression cytology, surface expression markers, blood or urine tests), nor patient reported outcome measures (visual analogue scales, ocular surface disease index (OSDI), 5-item Dry Eye Questionnaire (DEQ-5), visual function questionnaires) for recording the treatment effect of SED. Given the absence of specific information, recommendations are extrapolated from generic tools used for patients with ocular surface disease and as recommended by DEWS II, diagnostic methodology algorithm.[31 32]

6.6.3 Recommendation:

1. Instruments for assessment of the impact of treatment on health-related quality of life and objective grading of patient perceptions of disease using utility instruments specific for ocular surface disease, should be considered for use regularly in the clinical setting. These include the OSDI or the shorter DEQ-5. (Recommendation grade GPP).
2. Consistent recording of clinical outcome measures and scoring of disease should be considered. This includes visual acuity, meniscus height, presence of filaments, tear film break-up time, ocular surface staining score e.g. Ocular Staining Score, epithelial defect measurements (if present) and Schirmer's test without anaesthetic (Recommendation grade GPP).
3. It is advised that patients treated with Auto-SED and Allo-SED should be enrolled into a national programme. Frequency and duration of treatment together with serious adverse events should be recorded using a standard reporting procedure. A minimum follow-up of 6 months and then annually should be considered (Recommendation grade GPP).
4. Development and validation of SED-specific patient reported outcome tools and minimal clinical datasets for efficient outcome reporting is required. (Recommendation grade R)

7. Good Practice Points and Recommendations

Serum eye drops (SED) are an unlicensed medicinal product. These guidelines recommend that SED are beneficial for patients with acute and chronic severe ocular surface disease including patients with severe dry eye, persistent and recurrent corneal epithelial defects, neurotrophic keratopathy and for patients requiring supportive therapy for surgery. Severity should be defined with subjective and objective parameters and licensed treatments should be carefully considered before SED are prescribed. Monitoring of treatment effect with both patient and clinical reported outcomes is essential with specific consideration given for implementing treatment withdrawal and stopping strategies. Good practice includes clinical audit to document efficacy, safety, adverse reactions, and collection of data through a centralised patient registry to monitor longer term outcomes. Registry development and integration of direct and indirect costs to define effectiveness of treatment is recommended. Further research is required to determine bio-substance variability in serum donations, potential toxicity of autologous drops in some patients, identification of biomarkers for monitoring effectiveness, and determining optimal frequency, dosing and duration of SED treatment for each indication.

7.1 Clinical Indications for SED Treatment

- **MHRA REGULATORY NOTE:** SED are an unlicensed medicine. In accordance to the MHRA Guidance Note 14 (2014), supply of unlicensed medicinal products ("specials"), anyone supplying an unlicensed medicinal product, where an equivalent licensed medicinal product is available must be satisfied as to the existence of a special need for the unlicensed medicinal product. MHRA expects that documentary evidence of this special need should be obtained by manufacturers, importers or distributors and that this evidence should be made available on request of the Licensing Authority.
- ***Severe ocular surface disease:*** most common in Sjögren's syndrome (both primary and secondary to connective tissue diseases typically rheumatoid arthritis and systemic lupus erythematosis), immunobullous disorders usually mucous membrane pemphigoid, Stevens-Johnson syndrome, Graft versus Host Disease.
- ***Persistent and recurrent corneal epithelial defects:*** caused by dry eye disease, as well as other inflammatory ocular surface conditions, commonly severe allergic eye diseased, following corneal infections, limbal epithelial stem cell failure, neurotrophic keratitis.
- ***Neurotrophic keratopathy:*** this may be congenital, secondary to diabetic autonomic neuropathy, herpes zoster ophthalmicus, Vth cranial nerve tumours, non-ocular surgery/neurosurgery leading to corneal anaesthesia.
- ***Supportive therapy:*** for ocular surface reconstruction, patients in an intensive care setting with acute exposure keratopathy or toxic epidermal necrolysis, and those presenting with severe ocular surface injury such as chemical, thermal or radiation injury.

7.2 Patients Not Suitable for Serum Eye Drops

- **MHRA REGULATORY NOTE:** SED should not be supplied where an equivalent licensed medicinal product can meet the special needs of the patient. Responsibility for deciding whether an individual patient has "special needs" which a licensed product cannot meet should be a matter for the doctor responsible for the patient's care. Examples of "special needs" include an intolerance or allergy to a particular ingredient.
- Patients who have mild to moderate disease are not suitable for SED.

7.3 Eligibility Criteria

- All patients should meet clinically defined severity criteria according to the primary disease process and the doctor responsible for the management of the patent should have considered other available reversible causes/contributory factors and available licensed treatment options. The criteria described in the NHSE Specialised Service Circular SSC1728 March 2017 should be followed and are summarised in 7.3.1

7.3.1 Guidance scoring for disease severity:

- Severe, persistent ocular surface symptoms for > 1 year
- Patient severity score
  - Visual Analogue Score (0-10): >8
  - Ocular surface disease index (OSDI, Max 100): >33
- Tear film Break Up Time: <3 seconds
- Staining domains:
  - Van Bjisterveld score (Max 9) = 8 to 9
  - Ocular Surface Staining Score (Max 12) = 9 to 12
  - Oxford Staining Score (Max 15) = 11 to 15
- Persistent epithelial defect unresponsive to standard treatment

7.3.2 Therapeutic options prior to commencing SED

Treatment for patients with ocular surface disease should begin by implementing conservative self-help options and supplementary tears with non-preserved artificial substitutes, tear modification with acetylcysteine, where possible tear stimulation with pilocarpine, disease modification with anti- inflammatories and surface modification strategies. If there is absence of significant relief for the patient as measured by clinical and patient reported outcomes, SED may be considered as a therapeutic option. A combination of the following treatment approaches should be considered.

Please note the management options are not exhaustive.

- Conservative and Environmental Modification:
  - Local and general environmental modifications (e.g. moist chamber goggles, workplace modification including humidifiers).
  - Nutritional supplements such as Omega 3 and omega.
  - All comorbidities should be considered and optimised including lid margin disease, lid malposition, trichiasis and blepharospasm.
- Lubricants and Tear Substitution:
  - Basic lubricant preparations such as hypromellose, carbomer gels and ointments.
  - Regular, frequent non-preserved ocular lubricant including Hydroxypropylguar, hyaluronates (HA) and HA combinations (carboxymethylcellulose, polysaccharide, disaccharide or xanthan gum, soybean with phospholipids).
- Tear modification:
  - Acetylcysteine
  - Osmoprotectants
  - Liposomal sprays
- Tear Stimulation:
  - Use of secretagogues in incremental doses may be beneficial in selected cases e.g. oral pilocarpine.
- Disease Modification:
  - Topical anti-inflammatories such as non-preserved topical glucocorticoids, topical calcineurin inhibitors (NICE TA369 December 2015).
  - Systemic disease modifiers such as metallomatrix proteinase inhibitors e.g. sub-anti- microbial dose of antibiotics including low dose of tetracyclines and macrolides.
- Punctal Occlusion:
  - Punctal plugs and permanent cautery or occlusion (lower lid and then upper lid).
- Surface Modification:
  - Where possible therapeutic contact lenses (e.g. rigid gas permeable, soft hydrogel) provide a protective barrier to the ocular surface.
  - Rigid gas permeable scleral contact lenses are vaulted away from the ocular surface supported by the anterior sclera, enable a pre-corneal therapeutic reservoir to be created.

7.3.3 Specific considerations

For other clinical conditions such as recurrent corneal erosions, persistent epithelial defects, limbal epithelial stem cell failure, and ocular surface reconstruction, consider use of therapeutic contact lenses, corneal epithelial debridement, amniotic membrane graft to the cornea (including ProKera®, OmniLenz®), phototherapeutic laser, medical or surgical tarsorrhaphy as appropriate.

7.4 Autologous versus Allogeneic Treatment

1. Auto-SED should be considered for patients who are fit to donate one unit of blood, are able to travel to a blood donor centre, or the patient prefers auto-SED for personal, religious or cultural beliefs and do not wish to use donated serum.
2. Allo-SED should be considered in patients who are unable to donate one unit of blood such as those who are in poor general health, unable to attend a blood donor centre, less than age 16 years, or there is a clinical requirement for urgent treatment.
3. Allo-SED should be considered as an option in patients with uncontrolled diabetes, refractory immune-mediated diseases, those on cytotoxic agents where their bi-products are known to damage proliferating cells (e.g. cyclophosphamide) and patients with sepsis.
4. Frequency and duration of treatment depends upon individual circumstances. The doctor responsible for patient care should consider withdrawal and stopping strategies in all patients commenced on SED treatment before committing patients to indefinite treatment. Such strategies may include (i) withdrawal of treatment after one year of therapy in patients with ocular surface disease to define induction of remission before reinstating indefinite treatment if symptoms relapse, or (ii) in patients with persistent corneal epithelial defects, withdrawal of treatment after surface of the eye has healed and restoring treatment if the surface shows signs of breakdown. These are examples and this list should not be considered as exhaustive.

7.5 Monitoring

Treatment effect should be monitored with both patient and clinical reported outcome instruments both locally and in a centralised registry. This is essential for determining long term clinical and cost effectiveness of treatment. A web-based quality dashboard is considered best practice. Such tools detail frequency and duration of treatment together with record of serious adverse events using standard reporting procedures. Given the absence of evidence, a follow-up of 6 months and annual review should be considered.

Health related quality of life (HRQoL) burden increases with the severity of disease although disproportionate symptoms to signs (ocular neuropathic pain) is recognised. Objective grading of patient perceptions of disease using patient-reported outcome utility instruments specific for ocular surface disease is recommended e.g. the Ocular Surface Disease Index tool (**Appendix 2**). This is a 12 item questionnaire sub-divided into three domains: visual function (6); ocular symptoms (3); environmental triggers (3) where 0=no disability and 100= complete disability or the shorter 5-item Dry Eye Questionnaire (DEQ-5).

It is recommended that objective baseline clinical outcome tools are used. These tools should attempt to capture patient demographics as well as scoring of clinical signs to document response to treatment. Such data should include ethnicity and residential post code, centre details, confidentiality statement, date of treatment, clinical indication, type of serum eye drop treatment (autologous, allogeneic), clinical outcome measures and scores (visual acuity, meniscus height, presence of filaments, tear film osmolarity, tear film break-up time, ocular surface staining score, epithelial defect measurements (if present), Schirmer's test together with guides to standardise clinical methodology to record outcomes. (**Appendix 3**).

The follow-up outcome tool should be implemented after about 4-6 months of treatment. It should capture additional information such as whether the patient is still on treatment, has been transferred to another hospital, whether the treatment has been discontinued and whether there have been adverse local reactions or events (**Appendix 4**). There should be a record of whether other treatments (such as lubricants) were continued, reduced or withdrawn as they were no longer required. Ideally, longer term outcome data (1 year) to determine duration of treatment, or what proportion of patients are on indefinite duration treatment is required.

Recording of outcomes is a changing field. The example documents (**Appendix 2, 3 and 4**) are currently implemented by NHS BT. These will undergo controlled updates and if scales come into greater use and are practically validated, then they will be incorporated.

8. Further Research

The Guidelines development group recognises the need for further research. Several areas where further clinical trials or laboratory analyses have been identified are listed below. This list is not exhaustive.

1. Clinical trials comparing the clinical efficacy and cost effectiveness of autologous serum eye drops versus allogeneic serum eye drops are required.
2. Detailed serum constituent analyses of sequential donations from patient and healthy donors is required to interrogate bio-variability of each donation and the impact this could have on ocular surface health.
3. Further work on the development of protocols that reduce variability of biological constituents is required e.g. pooling of serum samples from multiple donors with measured ranges of main constituents.
4. Further research is required on the optimal formulation and diluent. This includes considering whether a 100% formulation is as effective as one that is diluted. A search for vehicles or carriers that improve the retention time and patient satisfaction is recommended.
5. Further work is required on the frequency and duration of serum eye drops treatment in each clinical indication. Clinical trials should specifically consider when it might be safe to implement treatment withdrawal in patients who have achieved measured success or remission according to pre-set defined criteria.
6. Development and validation of SED-specific patient reported outcome tools and minimal clinical datasets for efficient outcome reporting is required.

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10. Quick Guideline Reference

Which patient groups may benefit from serum eye drops (SED)?

- Severe ocular surface disease
  - Sjögren's syndrome (primary or secondary)
  - Immunobullous disorders (mucous membrane pemphigoid, Stevens-Johnson syndrome, Graft versus Host Disease)
- Persistent and recurrent corneal epithelial defects
- Neurotrophic keratopathy
  - Congenital, diabetic autonomic neuropathy, herpes zoster ophthalmicus, Vth cranial nerve tumours, non-ocular surgery/neurosurgery leading to corneal anaesthesia
- Supportive therapy
  - Ocular surface reconstruction
  - Patients in intensive care (e.g. exposure keratopathy, toxic epidermal necrolysis)
  - Acute severe ocular surface injury (e.g. chemical, thermal, radiation injury)

What is the difference between autologous (Auto-SED) or allogeneic (Allo-SED) serum eye drops?

- Auto-SED is made from a patient's own blood.
  - It should be considered for:
    - Patients who are fit to donate one unit of blood, have adequate venous access and can travel to a blood donor centre.
    - Patients who prefer auto-SED for personal, religious or cultural beliefs (i.e. do not wish to use donated serum).
- Allo-SED is made from individual (not pooled) male volunteer blood.
  - It should be considered when:
    - Patients are unable to donate one unit of blood (e.g. poor general health, unable to attend a blood donor centre).
    - There is a clinical requirement for urgent treatment.
    - Patients with uncontrolled diabetes, refractory immune-mediated diseases, those on cytotoxic agents where their bi-products are known to damage proliferating cells (e.g. cyclophosphamide) and patients with sepsis.

How should serum eye drops be prescribed?

- SED is an MHRA unlicensed medication (special), and should only be prescribed after licensed treatments have been considered or have been unsuccessful.
- Patient's disease severity should be defined with subjective and objective parameters, and be monitored throughout treatment to determine treatment response. It is recommended that monitoring occurs both locally and in a centralised registry.
- Auto-SED and Allo-SED as a 50% dilution in 0.9% Sodium chloride is recommended (as provided by the NHSBT, the only accredited SED production facility in the UK).
- Frequency and duration of treatment depends upon individual circumstances.
- Withdrawal and stopping strategies should be considered in all patients commenced on SED treatment before committing patients to indefinite treatment. For example:
  - In ocular surface disease: Withdrawal of treatment after one year of therapy to define induction of remission before reinstating indefinite treatment if symptoms relapse.
  - In persistent corneal epithelial defects: Withdrawal of treatment after surface of the eye has healed and restoring treatment if the surface shows signs of breakdown.

11. Appendices

11.1 Resources

11.1.1 Appendix 1: PICO Search Strategy

11.1.2 Appendix 2: Ocular Surface Disease Index Score

11.1.3 Appendix 3: Baseline clinical data

11.1.4 Appendix 4: Follow-up clinical data

11.2 Acknowledgements

The Royal College of Ophthalmologists would like to thank the Cochrane Eyes and Vision Group and in particular Iris Gordon for her assistance in searching the evidence base.

11.3 Details of the source of any funding

The development of this guideline was funded by The Royal College of Ophthalmologists

11.4 Details of the external peer-reviewers

This guidance was peer-reviewed through a formal consultation process where members of The Royal College of Ophthalmologists, Bowman Club, Ocular Tissue Advisory Group and British Society of Blood and Marrow Transplant were invited to provide comments. The draft guidance was available for wider consultation through publication on The Royal College of Ophthalmologists website, and final version was ratified through the Scientific Committee at The Royal College of Ophthalmologists.

11.5 Membership of the Guideline Development Group

- Mr Michael Burdon, Consultant Ophthalmologist, Queen Elizabeth Hospital Birmingham and The Royal College of Ophthalmologists
- Dr Akila Chandrasekar, Consultant in Transfusion Medicine, NHS Blood and Transplant Tissue Services
- Mrs Elizabeth Dancey, Patient representative and lead for the Serum Eye Drops Patient Focus and Support Group
- Professor Francisco Figueredo, Consultant Ophthalmologist, Newcastle Royal Victoria Infirmary
- Mr Barny Foot, The Royal College of Ophthalmologists
- Professor Stephen Kaye, Royal Liverpool University Hospital
- Miss Su-Yin Koay, OTG representative
- Dr Richard Lomas, Senior Development Clinical Scientist, NHS Blood and Transplant Tissue Services
- Miss Saaeha Rauz, Consultant Ophthalmologist, Birmingham and Midland Eye Centre and University of Birmingham - Chair of the Guidelines Development Group

11.6 Contribution of authors

The Multidisciplinary team involved in producing these guidelines was chaired by Miss Saaeha Rauz (Consultant Ophthalmologists specialising in ocular surface disease) who proposed and led the development of the guidelines. Miss Su-Yin Koay was involved in the grading of the evidence and providing summary tables. Mr Barny Foot represented The Royal College of Ophthalmologists Quality Team supported the guidance development. Professor Stephen Kaye and Professor Francisco Figueiredo provided Ocular Surface Specialist clinical input and Mr Michael Burdon provided general ophthalmology input and assured the guidance was

produced in accordance to The Royal College of Ophthalmologists Guidance Development Manual. Dr Akila Chandrasekar and Dr Richard Lomas represented NHS Blood and Transplant Tissue Services and provided source data from the SED service. Mrs Elizabeth Dancey contributed as a Patient and Carer representation and heads the Serum Eye Drops Patient Focus and Support Group.

12. Tables

Table 8: Characteristics and outcomes of clinical trials using blood products for ocular surface disease (Q1)

Reference	Patient characteristics	Type	Data Source	Number of eyes/patients	Intervention	Dilution (of intervention)	Frequency	Duration of treatment	Placebo	Concurrent therapy	PROM	Objective score	Level of evidence	Benefit
Pan et al 2017	DED (SS, nSS, post LASIK)	Cochrane systematic review	5 RCTs		Auto-SED						Improved symptoms in short term (2 weeks), but not sustained	Equivocal	1++	Positive/ Equivocal
Soni et al 2016	DED, PED	Systematic review	6 RCTs, 4 clinical reports		Auto-SED, Allo-SED, UCS, PRP						Improved OSDI	Improved TBUT, F and RB staining.	1++	Positive
Akpek et al 2011	SS	Review	3 clinical studies		Auto-SED						Equivocal	Equivocal	4	Equivocal
Azari et al 2015	PED, GVHD, DED, SS, RCE, aniridia	Review	46 clinical studies		Auto-SED						Suggested improvement	Improved	4	Positive
Ciralsky et al 2013	SJS, TEN	Review	2 clinical studies		Auto-SED						Not mentioned	improved	4	Positive
Celebi et al 2014	DED	Cross-over RCT		40 / 20	Auto-SED	20%	4x	1 month	Preservative free lubricants		Improved OSDI	Improved TBUT, Equivocal Schirmers	1+	Positive
Kojima et al 2005	DED (3), pSS (17)	Parallel RCT		37/ 20	Auto-SED	20% AutoSED	6x	2 weeks			Improved pain scores	Improved TBUT, F/ RB score. Equivocal Schirmers.	2++	Positive
Noda Tsuruya et al 2006	LASIK	Parallel RCT		27/54	Auto-SED	20% AutoSED	5x	6 months (started 1 week post op)	Softsantear (sodium chloride 0.1%)	0.3% hyaluronate 5x, 0.1% FML, Taravind antibiotics. All discontinued 1 week post op.	Equivocal subjective dryness scores	Improved TBUT and F staining. Equivocal Schirmers.	1+	Positive/ Equivocal
Urzua et al 2012	DED	Parallel RCT		12/12	Auto-SED	20% AutoSED	4x	2 weeks	Systane eye drops (Polyethylene Glycol 0.4% and Propylene Glycol 0.3%)		Improved OSDI	Improved TBUT and OXFORD staining (p>0.05)	1+	Positive/ Equivocal
Schulze et al 2006	Diabetics with corneal ED (post PPV)	Parallel RCT		13/13	Auto-SED	100% AutoSED	Hourly	Varied (until ED healed), max 14 days	0.18% sodium hyaluronate - Vislube	Isoptomax 4x, atropine 4x, neosynephrine 4x	Not assessed	SED quicker epithelisation	1+	Positive
Tanuvat et al 2001	DED (pSS,sSS, NHL, GVHD, SJS, RhA, idiopathic)	Parallel RCT		24/12	Auto-SED	20% AutoSED	6x	2 months	Unpreserved saline and dilute fluorescein	Lubricant eye drops	.	Improved F/RB staining. IC improved (p>0.05). Equivocal Schirmer/TBUT	2-	Positive/ Equivocal

DED: dry eye disease, SS: Sjögren's syndrome, pSS: primary Sjögren's syndrome, sSS: secondary Sjögren's syndrome, nSS: non-Sjögren's syndrome, PED: persistent epithelial defect, GVHD: graft versus host disease, RCE: recurrent corneal erosions, RhA: rheumatoid arthritis, NHL: non-Hodgkin's lymphoma. SED: serum eye drops, UCS: umbilical cord serum, PRP: platelet rich plasma. OSDI: ocular surface disease index, TBUT: tear break up time, F: fluorescein, RB: Rose Bengal

Table 9: Concentration of serum eye drops for the treatment of ocular surface disease (Q4)

Reference	Patient characteristics	Type	Intervention	Number of eyes/patients	Background treatment	Concentration	Duration of treatment	Frequency	Comments	PROM	Objective score	Level of evidence	Benefit
Cho et al 2013	pSS, nSS, PED	Prospective	Auto SED	42/22	Sodium hyaluronate 0.1% 4x	100% 50% (in Na0.9) 50% (in HA0.3) 50% (in Cef0.5)	12 weeks	6x	No difference re: what used for dilution	pSS: SED 100% improvement in OSDI nSS: No difference between SED 100% and 50%	pSS: SED 100% improved fluorescein staining vs all SED 50% nSS: SED 100% similar to SED 50% (Na0.9), SED 50% (Ha0.3) and 50% (Cef0.5) less effective. PED: SED 100% quickest epithelial closure	1+	Positive

pSS: primary Sjögren's syndrome, nSS: non Sjögren's syndrome, PED: persistent epithelial defect, SED: serum eye drops, Na0.9: sodium chloride 0.9%, HA 0.3: hyaluronic acid 0.3%, Cef0.5: ceftazidime

Appendix 1: PICO Search Strategy

Q1. Are SED more effective at treating patients with ocular surface disease, than conventional treatment?

Population	Intervention	Comparison	Outcome
Patients with Ocular Surface Disease	Serum Eye Drops	Conventional treatment	
Sjögren's Syndrome related dry eye, Mucous Membrane Pemphigoid, Stevens-Johnson-Syndrome, Graft Versus Host Disease, Ulcerative keratitis, neurotrophic cornea, diabetic cornea, persistent epithelial defects, ocular surface reconstruction surgery, supportive therapy	Serum or Cord Blood or Plasma or Blood Products AND Autologous or allogeneic AND eyedrops	Artificial Tears Ocular Lubricants Carmellose Hyaluronates	**Clinical** Ocular Surface Disease index, tear film break-up time, Schirmer's Test, Osmolarity, Oxford staining Score, Ocular Surface Staining Score, Visual acuity, Near Vison, Radner Read Speed **Laboratory** HLA DR2, impression cytology, cytokines, goblet cells, mucin, gene expression, proteonomics, metabolomics

Q2. Is there evidence of superiority in the cost and clinical effectiveness of autologous serum eye drops (Auto-SED) versus allogeneic serum eye drops (Allo-SED) at treating patients with ocular surface disease?

Population	Intervention	Comparison	Outcome
Patients with Ocular Surface Disease	Serum Eye Drops	Serum Eye Drops	
Sjögren's Syndrome related dry eye, Mucous Membrane Pemphigoid, Stevens-Johnson-Syndrome, Graft Versus Host Disease, Ulcerative keratitis, neurotrophic cornea, diabetic cornea persistent epithelial defects, ocular surface reconstruction surgery, supportive therapy	Autologous Serum Eye Drops	Allogeneic Serum Eye Drops Clinical Trial	**Clinical** Ocular Surface Disease index, tear film break-up time, Schirmer's Test, Osmolarity, Oxford staining Score, Ocular Surface Staining Score, Visual acuity, Near Vison, Radner Read Speed **Laboratory** - HLA DR2, impression cytology, cytokines, goblet cells, mucin, gene expression, proteonomics, metabolomics Direct Cost Indirect Cost EQ5D

Q3. What effect does dose size have on the effect of treatment with SED for patients with ocular surface disease?

Population	Intervention	Comparison	Outcome
Patients with Ocular Surface Disease	Serum Eye Drops		
Sjögren's Syndrome related dry eye, Mucous Membrane Pemphigoid, Stevens-Johnson-Syndrome, Graft Versus Host Disease, Ulcerative keratitis, neurotrophic cornea, diabetic cornea, persistent epithelial defects, ocular surface reconstruction surgery, supportive therapy	Autologous allogeneic Serum Eye Drops Dose	Clinical Trial, Case series, case reports	**Clinical** Ocular Surface Disease index, tear film break-up time, Schirmer's Test, Osmolarity, Oxford staining Score, Ocular Surface Staining Score, Visual acuity, Near Vison, Radner Read Speed **Laboratory** HLA DR2, impression cytology, cytokines, goblet cells, mucin, gene expression, proteonomics, metabolomics

Q4. What effect does concentration of formulation have on the effect of treatment with SED for patients with ocular surface disease?

Population	Intervention	Comparison	Outcome
Patients with Ocular Surface Disease	Serum Eye Drops		
Sjögren's Syndrome related dry eye, Mucous Membrane Pemphigoid, Stevens-Johnson-Syndrome, Graft Versus Host Disease, Ulcerative keratitis, neurotrophic cornea, diabetic cornea, persistent epithelial defects, ocular surface reconstruction surgery, supportive therapy	Autologous allogeneic Serum Eye Drops Formulation Concentration Dilution Preparation	Clinical Trial, case reports, series	**Clinical** Ocular Surface Disease index, tear film break-up time, Schirmer's Test, Osmolarity, Oxford staining Score, Ocular Surface Staining Score, Visual acuity, Near Vison, Radner Read Speed **Laboratory** HLA DR2, impression cytology, cytokines, goblet cells, mucin, gene expression, proteonomics, metabolomics

Q5. What effect does duration of treatment have on the effect of treatment with SED for patients with ocular surface disease?

Population	Intervention	Comparison	Outcome
Patients with Ocular Surface Disease	Serum Eye Drops		
Sjögren's Syndrome related dry eye, Mucous Membrane Pemphigoid, Stevens-Johnson-Syndrome, Graft Versus Host Disease, Ulcerative keratitis, neurotrophic cornea, diabetic cornea, persistent epithelial defects, ocular surface reconstruction surgery, supportive therapy	Autologous allogeneic Serum Eye Drops Duration Treatment	Clinical Trial, case reports, series	**Clinical** Ocular Surface Disease index, tear film break-up time, Schirmer's Test, Osmolarity, Oxford staining Score, Ocular Surface Staining Score **Laboratory** HLA DR2, impression cytology, cytokines, goblet cells, mucin, gene expression, proteonomics, metabolomics

Q6. What effect does frequency of treatment have on the effect of treatment with SED for patients with ocular surface disease?

Population	Intervention	Comparison	Outcome
Patients with Ocular Surface Disease	Serum Eye Drops		
Sjögren's Syndrome related dry eye, Mucous Membrane Pemphigoid, Stevens-Johnson-Syndrome, Graft Versus Host Disease, Ulcerative keratitis, neurotrophic cornea, diabetic cornea, persistent epithelial defects, ocular surface reconstruction surgery, supportive therapy	Autologous allogeneic Serum Eye Drops Duration Treatment Number of drops	Clinical Trial, case reports, series	**Clinical** Ocular Surface Disease index, tear film break-up time, Schirmer's Test, Osmolarity, Oxford staining Score, Ocular Surface Staining Score, Visual acuity, Near Vison, Radner Read Speed **Laboratory** HLA DR2, impression cytology, cytokines, goblet cells, mucin, gene expression, proteonomics, metabolomics

Q7. Which clinical outcome measures best record the treatment effect for monitoring ocular surface disease?

Population	Intervention	Comparison	Outcome
Patients with Ocular Surface Disease	Serum Eye Drops		
Sjögren's Syndrome related dry eye, Mucous Membrane Pemphigoid, Stevens-Johnson-Syndrome, Graft Versus Host Disease, Ulcerative keratitis, neurotrophic cornea, diabetic cornea, persistent epithelial defects, ocular surface reconstruction surgery, supportive therapy	Autologous allogeneic Serum Eye Drops	Clinical trials, case reports, series	**Clinical** Ocular Surface Disease index, tear film break-up time, Schirmer's Test, Osmolarity Anxiety, Depression, Quality of Life **Laboratory** HLA DR2, impression cytology, cytokines, goblet cells, mucin

Q8. Which patient reported outcome measures best record the treatment effect for monitoring impact on patient debility?

Population	Intervention	Comparison	Outcome
Patients with Ocular Surface Disease	Serum Eye Drops		
Sjögren's Syndrome related dry eye, Mucous Membrane Pemphigoid, Stevens-Johnson-Syndrome, Graft Versus Host Disease, Ulcerative keratitis, neurotrophic cornea, diabetic cornea, persistent epithelial defects, ocular surface reconstruction surgery, supportive therapy		Epidemiological studies, metanalysis, case reports, series	Ocular Surface Disease index (OSDI, NEI VFQ, Dry Eye Question (DEQ), impact of dry eye on everyday life (IDEEL) questionnaire, International Sjogren's classification, Hospital Anxiety and Depression Score

Appendix 2: Ocular Surface Disease Index Score

Circle the number in the box that best represents each answer.

Have you experienced any of the following *during the last week*?	**All of the time**	**Most of the time**	**Half of the time**	**Some of the time**	**None of the time**	
1. Eyes that are sensitive to light?	4	3	2	1	0	
2. Eyes that feel gritty?	4	3	2	1	0	
3. Painful or sore eyes?	4	3	2	1	0	
4. Blurred vision?	4	3	2	1	0	
5. Poor vision?	4	3	2	1	0	
				Subtotal score for answers 1 to 5. **A=**		

Have problems with your eyes limited you in performing any of the following *during the last week*?	**All of the time**	**Most of the time**	**Half of the time**	**Some of the time**	**None of the time**	**N/A**
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM	4	3	2	1	0	N/A
10. Watching TV?	4	3	2	1	0	N/A
				Subtotal score for answers 6 to 10. **B =**		

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	**All of the time**	**Most of the time**	**Half of the time**	**Some of the time**	**None of the time**	**N/A**
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned	4	3	2	1	0	N/A
				Subtotal score for answers 10 to 12. **C =**		

Add subtotals A, B and C to obtain D.

Total number of questions answered
(do not include questions answered N/A)

OSDI = [(sum of scores (D)) x 25]/(number of questions answered)

Appendix 3: Serum Eyedrop Clinical Outcome Recording – Baseline Data

This form may be completed online, or printed and completed by hand. Completed forms should be sent by email to richard.lomas@nhs.net or by post to: Serum Eyedrop Follow Up, Tissue Services, NHSBT Liverpool, 14 Estuary Banks, Liverpool L24 8RB.

If you are returning forms by email, **please only send them from an 'nhs.net' email address**, to ensure the security of confidential patient data. Please call 0845 607 6820 if you have any queries

Patient Reference Number: *(NHSBT Use Only)*	

PART 1: PATIENT DETAILS

Recipient Surname		Recipient Forename:			
Date of birth (DD/MM/YYYY)		Male	☐	Female	☐
NHS No.		Date of treatment start (DD/MM/YYYY)			
Ethnicity		White	☐		
		Asian or Asian British	☐		
		Black or Black British	☐		
		Chinese or Oriental	☐		
		Mixed (please specify)	☐		
		Other (please specify)	☐		
If selecting 'Mixed' or 'Other' ethnicity, please give further details					
First half of postcode					

PART 2: CENTRE DETAILS

Hospital name		Hospital No.	
Consultant		Form completed by	
Date of completion (DD/MM/YYYY)			

PART 3: CONFIDENTIALITY STATEMENT

Consent for use of patient data	Full ☐	Partial ☐	Refused(1) ☐
If selecting 'partial', please specify data for which consent is NOT given			

(1) If consent for use of data is refused, please complete this form up to and including Part 5 and return to NHSBT. No further follow up will be requested for the patient.

PART 4: TREATMENT

Type of serum prescribed	Autologous ☐	Allogeneic ☐

PART 5: INDICATION(S)

Please specify the **one** clinical indication for which serum eyedrops have been prescribed, using the codes in Annex 1	
If the precise indication is not specified, or you have selected an 'other' category, please give further details	

(Template Version 01/11/13)

Serum Eyedrop Clinical Outcome Recording – Baseline Data

PART 6: CLINICAL OUTCOME MEASURES AND SCORES

Please conduct all tests in the order specified

		Right eye		Left eye	
1	Visual acuity (Snellen) – Best corrected				
2	Visual acuity (Snellen) – Near vision				
3	Meniscus	Normal	☐	Normal	☐
		Reduced	☐	Reduced	☐
4	Filaments	None	☐	None	☐
		Present	☐	Present	☐
5	If available – Tear film osmolality (mOsm/L)				

		Right eye	Left eye
6	Tear film break up time (s) – use DEWS standardised methodology as per Annex 2		
7	Exposed Ocular Surface Staining (Oxford Schema) – use DEWS standardised methodology as per Annex 3		

8	Persistent corneal epithelial defect measurement				
Right eye	None	☐	Left eye	None	☐
	Present	☐		Present	☐
Size (mm)	Min:		Size(mm)	Min:	
	Max:			Max:	

		Right eye	Left eye
9	Schirmer Test 1 without anaesthetic (mm) – use DEWS standardised methodology as per Annex 4		

PART 7: ADDITIONAL NOTES

Serum Eyedrop Clinical Outcome Recording – Baseline Data

ANNEX 1 – CLINICAL INDICATION CODE

PLEASE SELECT ONE INDICATION

Main Category	Subcategory	Code
Sjogren's related dry eye		**A**
Other immune related dry eye	Ocular Mucous Membrane Pemphigoid	**B1**
	Stevens Johnson-Syndrome/Toxic Epidermal Necrolysis	**B2**
	Graft-versus-Host Disease	**B3**
	Other immune related dry eye	**B4**
Non-immune dry eye	Meibomian Gland Disease	**C1**
	Other non-immune dry eye	**C2**
Neurotrophic disease	Diabetic Cornea	**D1**
	Herpetic aetiology	**D2**
	Other neurotrophic disease	**D3**
Injury/Trauma	Ocular Surface Toxicity	**E1**
	Chemical	**E2**
	Thermal	**E3**
	Mechanical	**E4**
	Radiation	**E5**
	Surgical (e.g. LASIK)	**E6**
	Other injury/trauma	**E7**
Exposure Keratopathy	ITU/HDU Patient	**F1**
	Thyroid Associated Ophthalmopathy	**F2**
	Non-Thyroid Proptosis	**F3**
	Other exposure keratopathy	**F4**
Supportive	Ocular Surface Reconstruction	**G1**
	Corneal Transplant	**G2**
	Other Supportive	**G3**
Inherited Ocular Surface Disease	Aniridia	**H1**
	Ectodermal Dysplasia	**H2**
	Epidermolysis Bullosa	**H3**
	Other Inherited Ocular Disease	**H4**

Serum Eyedrop Clinical Outcome Recording – Baseline Data

ANNEX 2: TEAR FILM BREAK UP TIME

CONDUCT OF TEST

1. Instill 1 to 5 micro-litres of non-preserved, 2% sodium flourescein onto the bulbar conjuctiva, without inducing reflex tearing, by using a micro-pipette or D.E.T strip.

2. Instruct the patient to blink naturally, without squeezing, several times to distribute the flourescein.

3. Within 10-30 seconds of the flourescein instillation, ask the patient to stare straight ahead without blinking, until told otherwise

4. Set slit-lamp magnification at 10x, keep the background illumination intensity constant (cobalt blue light) and use a Wratten 12 yellow filter to enhance observation of the tear film over the entire cornea.

5. Use a timer to record the time between the last complete blink and the first appearance of a growing micelle.

6. Once TFBUT is observed, instruct the patient to blink freely.

ITEMS REQUIRED

- Non-preserved, 2% sodium flourescein
- Micro-pipette or D.E.T strip
- Slit lamp
- Timer
- Kodak Wratten filter 12

NOTES

1. It is important to standardise the following criteria as closely as possible:

- Time day
- Temperature
- Humidity
- Air speed
- Illumination
- Patient instruction
- Slit-lamp magnification
- Barrier filter

2. Instillation of flourescein must be done carefully so that reflex tearing is not induced. Alterations in tear volume may artificially lengthen TFBUT.

3. Proper patient instruction is critical. If patients are not told to blink freely after TFBUT occurs, reflex tearing may occur and skew subsequent measurements.

4. Large, uncontrolled volumes of flourescein may also artificially lengthen TFBUT

Serum Eyedrop Clinical Outcome Recording – Baseline Data

ANNEX 3: EXPOSED OCULAR SURFACE SCORE (OXFORD SCHEMA)

CONDUCT OF TEST

1. Instill the dye

2. Set the slit lamp

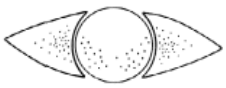
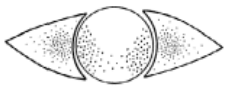
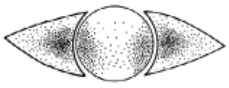
3. Lift the upper eyelid slightly to grade the whole corneal surface

4. Ask to patient to look nasally to grade the temporal zone, and temporally to grade the nasal zone

ITEMS REQUIRED

- Oxford grading panel (Figure 1 below)
- Slit-lamp
- Selected dye

FIGURE 1 – OXFORD GRADING SCHEME

PANEL	Grade	Criteria
A 	0	Equal to or less than panel A
B 	I	Equal to or less than panel B, greater than A
C 	II	Equal to or less than panel C, greater than B
D 	III	Equal to or less than panel D, greater than C
E 	IV	Equal to or less than panel E, greater than D
>E	V	Greater than panel E

Staining is represented by punctuate dots on a series of panels (A-E). Staining ranges from 0-5 for each panel and 0-15 for the total exposed inter-palpebral conjunctiva and cornea. The dots are ordered on a log scale.

NOTES ON DYE SELECTION

This test can be performed with flourescein, rose bengal or lissamine green. With flourescein, staining must be graded as quickly as possible after installation, since the dye then diffuses rapidly into the tissue and it's high luminosity blurs the staining margin. After staining with rose bengal or lissamine green, the stain persists at high contrast and may therefore be observed for a considerable period. This is convenient for both grading and photography.

Serum Eyedrop Clinical Outcome Recording – Baseline Data

ANNEX 4: SCHIRMER TEST 1 – WITHOUT ANAESTHETIC

CONDUCT OF TEST

1. Insert the paper strip over the lower eyelid margin, midway between the middle and outer third

2. Instruct the patient to close the eye

3. Read the strip after 5 minutes

ITEMS REQUIRED

- Schirmer papers (5x35mm Whatman No. 1)

NOTES

1. It is important to standardise the following criteria as closely as possible:

- Time day
- Temperature
- Humidity
- Air speed
- Illumination

Appendix 4: Serum Eyedrop Clinical Outcome Recording – Follow Up Data

This form may be completed online, or printed and completed by hand. Completed forms should be sent by email to richard.lomas@nhs.net or by post to: Serum Eyedrop Follow Up, Tissue Services, NHSBT Liverpool, 14 Estuary Banks, Liverpool L24 8RB.

If you are returning forms by email, **please only send them from an 'nhs.net' email address**, to ensure the security of confidential patient data.

Please call 0845 607 6820 if you have any queries

Patient Reference Number: *(NHSBT Use Only)*	

PART 1: PATIENT DETAILS

Recipient Surname		Recipient Forename:			
Date of birth (DD/MM/YYYY)		Male	☐	Female	☐
NHS No.		Date of treatment start (DD/MM/YYYY)			

Is the patient still attending your clinic?	Yes	☐	No	☐
If answering 'no', please specify the reason:	Patient transferred to another hospital			☐
	Lost to follow up			☐
	Died			☐

PART 2: CENTRE DETAILS

Hospital name		Hospital No.	
Consultant		Form completed by	
Date of completion (DD/MM/YYYY)			

PART 3: FOLLOW UP

Date of follow up examination				
Which type of serum eyedrop is the patient currently using?	Autologous	☐	Allogeneic	☐

Serum Eyedrop Clinical Outcome Recording – Follow Up Data

PART 4: CLINICAL OUTCOME MEASURES AND SCORES

Please conduct all tests in the order specified

		Right eye		Left eye	
1	Visual acuity (Snellen) – Best corrected				
2	Visual acuity (Snellen) – Near vision				
3	Meniscus	Normal	☐	Normal	☐
		Reduced	☐	Reduced	☐
4	Filaments	None	☐	None	☐
		Present	☐	Present	☐
5	If available – Tear film osmolality (mOsm/L)				

6	Global question: Has the treatment with Serum Eyedrops improved the quality of your patient's life? (Please tick one box)										
0 (Back to normal)	1	2	3	4	5	6	7	8	9	10 (No change)
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

		Right eye	Left eye
7	Tear film break up time (s) – use DEWS standardised methodology as per Annex 1		
8	Exposed Ocular Surface Staining (Oxford Schema) – use DEWS standardised methodology as per Annex 2		

9	Persistent corneal epithelial defect measurement					
Right eye	None	☐	Left eye	None	☐
	Present	☐		Present	☐
Size (mm)	Min:		Size(mm)	Min:	
	Max:			Max:	

		Right eye	Left eye
10	Schirmer Test 1 without anaesthetic (mm) – use DEWS standardised methodology as per Annex 3		

Serum Eyedrop Clinical Outcome Recording – Follow Up Data

PART 5: COMPLICATIONS OR REASONS FOR DISCONTINUATION

5(i) - DISCONTINUATION

Has treatment been discontinued?	Yes	☐	No	☐
If so, please specify why:	Intolerance			☐
	Completed prescribed course			☐
	No benefit			☐
	Other (please specify)			☐
If selecting other, please specify:				

5(ii) ADVERSE REACTIONS

Have any **adverse reactions**(1) been noted?	Yes	☐	No	☐
If answering 'yes' please specify:	Infection (microbial keratitis)			☐
	Other (please specify)			☐
If selecting other, please specify:				

5(iii) ADVERSE EVENTS

Have any **adverse events**(1) been noted?	Yes	☐	No	☐
If answering 'yes' please provide details:				

(1) – Please report any adverse reactions or adverse events to NHSBT **immediately** on 0845 607 6820

PART 6: ADDITIONAL NOTES

Serum Eyedrop Clinical Outcome Recording – Follow Up Data

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ITEMS REQUIRED

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- Timer
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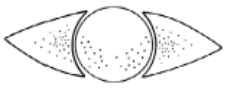
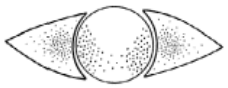
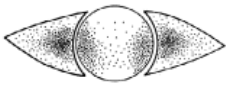
C 	II	Equal to or less than panel C, greater than B
D 	III	Equal to or less than panel D, greater than C
E 	IV	Equal to or less than panel E, greater than D
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Serum Eyedrop Clinical Outcome Recording – Follow Up Data

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- Illumination

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