Pwyllgor Gwasanaethau Iechyd Arbenigol Cymru (PGIAC)
Welsh Health Specialised Services Committee (WHSSC)

Specialised Services Policy:
CP91
Extracorporeal Photophoresis (ECP) for the Treatment of Chronic Graft versus Host Disease in Adults

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Policy Statement

Background	**Extracorporeal photophoresis (ECP)** is a form of apheresis and photodynamic therapy in which blood is treated with a photosensitizing agent and subsequently irradiated with specified wavelengths of light to achieve an effect. Specifically, buffy coat (white blood cells plus platelets) is separated from whole blood, chemically treated with 8-methoxypsoralen, exposed to ultraviolet light, and returned to the patient. **Graft versus host disease (GvHD)** is a major complication of haematopoietic stem cell transplantation (commonly known as blood and marrow transplant or BMT).
Summary of Access Criteria	The Welsh Health Specialised Services Committee (WHSSC) will fund extracorporeal photophoresis (ECP) for the treatment of chronic graft versus host disease in line with the treatment criteria and indications outlined in this policy. This policy does not apply to acute graft versus host disease and therefore WHSSC requires prior approval for each patient to be agreed for funding for this condition. The evidence and response rates for ECP in chronic GvHD affecting only the liver, lung and gasterointestinal tract is variable and funding is not agreed in this context.
Responsibilities	NHS Blood and Transplant must ensure that patients are treated in accordance with the Policy and supply the data as specified in Annexes i and ii. The referring clinician must use the Policy to advise patients of the treatment options and refer patients in line with the Policy.

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1. Aim

1.1 Introduction

The document is the commissioning policy for Extracorporeal Photophoresis (ECP) for the treatment of Chronic Graft versus Host Disease (cGvHD) in adults for Welsh patients. The policy applies to residents of all seven Health Boards in Wales and English residents with a Welsh GP.

The purpose of this document is to:

- Set out the circumstances under which patients will be able to access ECP for the treatment of chronic graft versus host disease in adults;
- clarify the referral process; and
- define the criteria that patients must meet in order to access treatment.

The Policy also clarifies the funding arrangements for ECP for acute Graft versus Host Disease.

1.2 Relationship with other Policies and Service Specifications

This document should be read in conjunction with the following documents:

- All Wales Policy: Making Decisions on Individual Patient Funding Requests (IPFR).

2. Scope

2.1 Definition

Extracorporeal Photophoresis (ECP) ECP is a form of apheresis and photodynamic therapy in which blood is treated with a photosensitizing agent and subsequently irradiated with specified wavelengths of light to achieve an effect. Specifically, buffy coat (white blood cells and platelets) is separated from whole blood, chemically treated with 8-methoxypsoralen, exposed to ultraviolet light, and returned to the patient.

Chronic Graft versus Host Disease (cGvHD) Graft versus host disease is a major complication of haematopoietic stem cell transplantation. Immune cells (white blood cells) in the tissue (the graft) recognise the recipient (the host) as "foreign". The transplanted immune cells then attack the host's body cells. There are two types of GvHD; acute and chronic. Diagnosis should be made using the international consensus guidelines published by the National Institutes of Health (2010-2014) in which clinical features are used to determine if the clinical syndrome of GvHD is acute or chronic, not the time after transplantation. The NIH guidelines also include a graded scoring mechanism for the severity of the disease and a consensus statement on treatment.

Chronic graft-versus-host disease (cGvHD) is a serious and common complication of allogeneic hematopoietic cell transplantation (commonly known as blood and marrow tranplant or BMT), occurring in 30% to 70% of patients. Chronic GVHD is a syndrome with variable clinical features which may resemble other autoimmune or immunologic disorders that may occur later after BMT. Clinical manifestations nearly always present during the first year after transplantation, but in some cases they can develop many years after the BMT. Manifestations of chronic GVHD may be restricted to a single organ or site, or may be widespread, with profound impact on quality of life. Like acute GVHD, chronic GvHD may affect the skin, gut, liver or mouth but can also affect other parts of the body, such as the eyes, lungs, genitalia and joints. Chronic GVHD may be mild or severe, and can last for several months or years. Chronic GvHD is one of the major causes of late transplant-related mortality after a BMT.

2.2 Codes

ICD-10 Codes

Code	Description
T86.0	Bone marrow transplant rejection Graft versus host disease

3. Access Criteria

3.1 Criteria and Indications for Treatment

The criteria for treatment are shown below. These should be established through an assessment as specified in section 3.3:

1. A stem cell transplant physician is responsible for supervising the treatment of the patient for their chronic graft-versus-host disease (GvHD);
2. The patient has chronic GvHD which has been diagnosed using the National Institutes of Health (NIH) international consensus guidelines (2014) which standardises the criteria for diagnosis of chronic graft-versus-host disease;
3. The patient must have skin or mucosal (mouth) involvement (either in isolation or in combination with other organs);
4. The patient is refractory to standard therapy (topical therapy, systemic corticosteroids) or advanced therapy (anti-tumour necrosis factor antibodies, mammalian target of rapamycin (mTOR)inhibitors, mycophenolate mofetil, interleukin-2 receptor antibodies, immunosuppression therapy); and,
5. The patient's disease is not in one of the excluded categories detailed in section 3.2.

3.2 Exclusions

This policy does not apply to ECP for acute GvHD which is funded through prior approval on an individual patient basis only.

The evidence and response rates for ECP in chronic GvHD affecting only the liver, lung and gasterointestinal tract is variable and funding is not agreed in this context.

There is limited evidence for ECP in autoimmune diseases and the other indications listed below. Funding for these conditions has not been approved:

- Autoimmune diseases including systemic sclerosis, systemic lupus erythematosus, scleromyxedema, nephrogenic fibrosing dermopathy/nephrogenic systemic sclerosis, rheumatoid arthritis;
- Type 1 diabetes mellitus;
- Pemphigus vulgaris;
- Epidermolysis bullosa acquisita;
- Atopic dermatitis;
- Inflammatory bowel disease;
- Multiple sclerosis;
- Chronic hepatitis C; and,
- Psoriasis.

3.3 Treatment and referral Pathway

If a BMT Consultant has made a diagnosis of chronic GvHD according to the NIH guidelines and considers that ECP treatment would be of benefit to the patient, and the patient meets the indications and access criteria in this Policy, the Consultant can make a referral for extracorporeal photophoresis. The provider is NHS Blood and Transplant, based at The Christie NHS Foundation Trust in Manchester (with satellite units at Royal Liverpool University Hospital and Manchester Royal Infirmary) for North Wales residents, and at the University Hospitals Bristol NHS Foundation Trust for South Wales residents.

On receipt of the referral an appointment will be made for the patient to be seen at the NHSBT centre. At this appointment various blood tests will be carried out and the patient will be assessed to ensure their suitability for treatment.

If the assessment confirms that the patient meets the criteria and indications, the patient can proceed to treatment under the SLA with WHSSC. NHSBT must apply the review schedule and stopping criteria as outlined in this Policy.

First Appointment at ECP Centre:

- Medical history and clinical examination;
- Drug history, including use of corticosteroids;
- Skin assessment: skin score, pruritus (itch) score;
- Eye assessment: Schirmer's Test (test of tear production);
- Mouth assessment;
- Gastrointestinal assessment;
- Joint assessment: if required;
- Blood tests;
- Respiratory assessment (breathing tests);
- Medical photography;
- Karnovsky's scale (self assessment measure of patient's activity);
- Quality of life assessment (self assessment measure of patient's quality of life); and,
- NIH chronic GvHD diagnosis and severity score.

Every three months:

- Medical history since last review;
- Drug history since last review, including use of corticosteroids;
- Pruritus (itch) score;
- Eye assessment;
- Mouth assessment;
- Gastrointestinal assessment;
- Joint assessment if required;
- Blood tests;
- Karnovsky's scale; and,
- NIH chronic GvHD diagnosis and severity score.

3.4 Treatment Cycle for Chronic GvHD

The recommended treatment cycle is one cycle (two treatments on consecutive days) every two weeks.

The therapy should be undertaken for a period of three months at which stage the clinical success of the treatment will be determined as in section 3.5 and 3.6.

3.5 Treatment Review Schedule for Chronic GvHD

Every 3 Months:

- Partial response or maximal response: reduce to one cycle every 4 weeks.
- Complete response: stop therapy.
- Minimal response, stable disease or progressive disease: stop therapy.

Form 2 in Annex i must be completed and returned to WHSSC after each review. WHSSC will not fund treatment after the first 3 months of the start date for any patient if a review form documenting the justification for the continuing treatment is not received. These must be received every 3 months.

The definition of 'response' is shown in section 3.6.

3.6 Stopping Criteria

Definition of 'response'.

1. Complete response - resolution of active GVHD manifestations without systemic immunosuppression.
2. Partial response - > 50% improvement of organ involvement scores (skin, liver or oral mucosa) from baseline investigation and / or > 50% reduction in immunosuppression.
3. Minimal response - < 50% improvement of organ involvement scores (skin, liver or oral mucosa) from baseline investigation and / or 25-50% reduction in immunosuppression.

4. Stable disease - no improvement of organ involvement scores (skin, liver or oral mucosa) from baseline investigation and no reduction in immunosuppression.

5. Progressive disease - worsening of organ involvement scores (skin, liver or oral mucosa) from baseline investigation or new disease in previously unaffected organ or increase in immunosuppression.

6. Maximal response - partial response stable for 3 months with reduced or stable immunosuppression.

3.7 Audit of Policy Application

NHSBT must supply audit data to assure WHSSC of the application of the Policy on a quarterly basis. If this audit data is not supplied, or shows that the Policy is not being applied correctly, WHSSC will revert to a Prior Approval mechanism for funding for all cases.

If the patient wishes to be referred to a provider out of the agreed pathway, an IPFR should be submitted.

3.8 Exceptions

If the patient does not meet the criteria for treatment, but the referring clinician believes that there are exceptional grounds for treatment, an Individual Patient Funding Request (IPFR) can be made to WHSSC under the *All Wales Policy for Making Decisions on Individual Patient Funding Requests (IPFR)*.

If the patient wishes to be referred to a provider out of the agreed pathway and the referring clinician believes that there are exceptional grounds for treatment at an alternative provider, an Individual Patient Funding Request (IPFR) can be made to WHSSC under the *All Wales Policy for Making Decisions on Individual Patient Funding Requests (IPFR)*.

Guidance on the IPFR process is available at www.whssc.wales.nhs.uk

3.9 Responsibilities

NHS Blood and Transplant

NHSBT must ensure that patients are treated in accordance with this Policy and supply the audit data specified in Annex i.

NHSBT must also supply the required clinical ausit and quality data to WHHSC on annual basis. This is specified in Annex ii.

Referring Clinician

The referring clinician must use the Policy to advise patients of their treatment options and refer patients in accordance with the Policy.

If the patient meets the criteria but wants to be referred to a non-contract provider an IPFR request must be completed and sent to WHSSC for approval of funding before treatment commences.

If the patient does not meet the criteria but there is evidence of exceptionality, an IPFR request must be completed and sent to WHSSC for approval of funding before treatment commences.

4. Putting Things Right: Raising a Concern

Whilst every effort has been made to ensure that decisions made under this policy are robust and appropriate for the patient group, it is acknowledged that there may be occasions when the patient or their representative are not happy with decisions made or the treatment provided. The patient or their representative should be guided by the clinician, or the member of NHS staff with whom the concern is raised, to the appropriate arrangements for management of their concern:

- When a patient or their representative is unhappy with the decision that the patient does not meet the criteria for treatment further information can be provided demonstrating exceptionality. The request will then be considered by the All Wales IPFR Panel.
- If the patient or their representative is not happy with the decision of the All Wales IPFR Panel the patient and/or their representative has a right to ask for this decision to be reviewed. The grounds for the review, which are detailed in the All Wales Policy: Making Decisions on Individual Patient Funding Requests (IPFR), must be clearly stated. The review should be undertaken, by the patient's Local Health Board;
- When a patient or their representative is unhappy with the care provided during the treatment or the clinical decision to withdraw treatment provided under this policy, the patient and/or their representative should be

guided to the LHB for NHS Putting Things Right. For services provided outside NHS Wales the patient or their representative should be guided to the NHS Trust Concerns Procedure, with a copy of the concern being sent to WHSSC.

5. Equality Impact and Assessment

The Equality Impact Assessment (EQIA) process has been developed to help promote fair and equal treatment in the delivery of health services. It aims to enable Welsh Health Specialised Services Committee to identify and eliminate detrimental treatment caused by the adverse impact of health service policies upon groups and individuals for reasons of race, gender re-assignment, disability, sex, sexual orientation, age, religion and belief, marriage and civil partnership, pregnancy and maternity and language (welsh).

This policy has been subjected to an Equality Impact Assessment. The Assessment demonstrates the policy is robust and there is no potential for discrimination or adverse impact. All opportunities to promote equality have been taken.

Annex (i) Audit of Application of Policy

The following forms should be completed and submitted to WHSSC by NHSBT.

Form 1. New patient

Patient NHS No:		
Patient is Welsh Resident	Post Code	
Patient is English Resident registered with NHS Wales GP	GP Code	

Patient meets the following access criteria and indications for treatment:	**Yes**	**No**
A stem cell transplant physician is responsible for supervising the treatment of the patient for their chronic graft-versus-host disease (GvHD).		
The patient has chronic GvHD which has been diagnosed and severity rated using the latest published version of National Institutes of Health (NIH) international consensus guidelines.		
The patient must have skin or mucosal involvement (either in isolation or in combination with other organs).		
The patient is refractory to standard therapy (topical therapy, systemic corticosteroids) or advanced therapy (anti-tumour necrosis factor antibodies, mammalian target of rapamycin (mTOR)inhibitors, mycophenolate mofetil, interleukin-2 receptor antibodies, immunosuppression therapy).		
The patient's disease is not in one of the excluded categories detailed in section 3.2.		
Patient assessment has been carried out as in section 3.3.		
Patient is eligible for funding based on the Policy requirements .		

Date patient starts treatment .....

Form 2. Review Patient

Patient NHS No:		
Patient is still a Welsh Resident	Post Code	
Patient is still an English Resident registered with NHS Wales GP	GP Code	

Dates	
Date patient started treatment	
Review Date	

Application of Stopping Criteria		
Response	**Yes**	**No**
Complete response - resolution of active GVHD manifestations without systemic immunosuppression		
Partial response - > 50% improvement of organ involvement scores (skin, liver or oral mucosa) from baseline investigation and / or > 50% reduction in immunosuppression		
Minimal response - < 50% improvement of organ involvement scores (skin, liver or oral mucosa) from baseline investigation and / or 25-50% reduction in immunosuppression		
Stable disease - no improvement of organ involvement scores (skin, liver or oral mucosa) from baseline investigation and no reduction in immunosuppression		
Progressive disease – worsening of organ involvement scores ((skin, liver or oral mucosa) from baseline investigation or new disease in previously unaffected organ or increase in immunosuppression		
Maximal response – partial response, stable for 3 months with reduced or stable immunosuppression		
Action Taken		
Continued Treatment		
Reduction to one cycle every four weeks		
Stopped treatment		

Annex (ii) Clinical Audit and Quality Criteria

Clinical Audit

A clinical audit will be required on an annual basis from NHS Blood and Transplant which will include the following:

- A summary of all patients and their response to treatment classified as:
  1. Complete response - resolution of active GVHD manifestations without systemic immunosuppression;
  2. Partial response - > 50% improvement of organ involvement scores (skin, liver or oral mucosa) from baseline investigation and / or > 50% reduction in immunosuppression;
  3. Minimal response - < 50% improvement of organ involvement scores (skin, liver or oral mucosa) from baseline investigation and / or 25-50% reduction in immunosuppression;
  4. Stable disease - no improvement of organ involvement scores (skin, liver or oral mucosa) from baseline investigation and no reduction in immunosuppression;
  5. Progressive disease - worsening of organ involvement scores (skin, liver or oral mucosa) from baseline investigation or new disease in previously unaffected organ or increase in immunosuppression;
  6. Maximal response - partial response stable for 3 months with reduced or stable immunosuppression.
- A summary of patients' NIH cGVHD severity rating before and after treatment.
- A summary of compliance with the Policy.
- An annual audit of quality of life using EQ-5D, SF-6D or similar changes before and after treatment.
- Patient Experience measured by the CAREs tool (http://www.caremeasure.org/) and a summary of complaints and compliments.

Serious Incidents

Deaths and serious adverse events must be reported in real time (48 hours following the event) directly to the Medical Director and Director of Nursing, WHSSC.