MSAC Application

Integrated, closed-system, extracorporeal photopheresis and methoxsalen (UVADEX®) for chronic graft versus-host-disease, update to MBS and PBS items

PICO Set (1)

Table of Abbreviations

ARTG	Australian Register of Therapeutic Goods
BOS	Bronchiolitis obliterans syndrome
CT	Computed tomographic
ECP	Extracorporeal photopheresis
EDF	European Dermatology Forum
GVHD	Graft versus-host-disease
HSC	Haematopoietic stem cell
HSCT	Haematopoietic stem cell transplantation
MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NIH	National Institutes of Health
PASC	PICO Advisory Subcommittee
PBS	Pharmaceutical Benefits Scheme
PFT	Pulmonary function test
PUVA	Psoralen plus ultraviolet A radiation
RBC	Red blood cells
SAS	Special Access Scheme
UK	United Kingdom
UV	Ultraviolet
UVA	Ultraviolet A
WBC	White blood cells

Population

Describe the population in which the proposed health technology is intended to be used:

Due to the nature of this application the population is unchanged from those currently approved for treatment with extracorporeal photopheresis (ECP) under Medicare Benefits Schedule (MBS) items 13761 and 13762.

In summary, the proposed health technology is intended for use in Australian adults with a confirmed diagnosis of chronic graft versus-host-disease (cGVHD) following haematopoietic stem cell transplantation (HSCT) who are:

- clinically unsuitable for steroid treatment as the disease is steroid-refractory, or the person is steroid-dependent or intolerant
- receiving the treatment in combination with use of ex-vivo injectable methoxsalen.

Specify any characteristics of patients with, or suspected of having, the medical condition, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian healthcare system in the lead up to being considered eligible for the technology:

Graft versus-host-disease (GVHD) is a severe complication that can occur following HSCT. This condition arises when immunocompetent T lymphocytes from the donor graft recognise the recipient's tissues as foreign due to histocompatibility differences and initiate an immune response against them (Ferrara et al. 2009; Welniak et al. 2007). This attack typically leads to tissue damage in various organs, including the skin, gastrointestinal tract, liver, and lungs.

Acute versus chronic GVHD

Historically, the distinction between acute GVHD (aGVHD) and chronic GVHD (cGVHD) was based on whether diagnosis occurred before or after 100 days post-transplant. The 2005 National Institutes of Health (NIH) Consensus Conference redefined aGVHD and cGVHD as distinct clinical syndromes without a strict time cutoff (Lee 2017), a definition reaffirmed by the NIH Consensus Conference in 2014 (Jagasia et al. 2015). Under this framework, aGVHD is characterised by the inflammatory involvement of the skin, liver, and gastrointestinal tract, and may occur either before or after 100 days post-transplant. cGVHD instead manifests as an autoimmune-like, multi-organ condition and may arise de novo, evolve from aGVHD, or develop following its resolution. Clinically, cGVHD is based on organ-specific findings defined in the NIH consensus report (Jagasia et al. 2015). Affected organs include skin, liver, lungs, oral mucosa, and eyes, and symptoms reflect chronic immune dysregulation, often presenting similar to systemic autoimmune disease (van der Wagen et al. 2018; Wood et al. 2013). cGVHD is associated with prolonged immunosuppression, reduced quality of life, and increased non-relapse mortality (Berger et al. 2015; Wood et al. 2013). A detailed synopsis of these clinical features for different organs is presented in Appendix A.

Management and referral prior to extracorporeal photopheresis eligibility

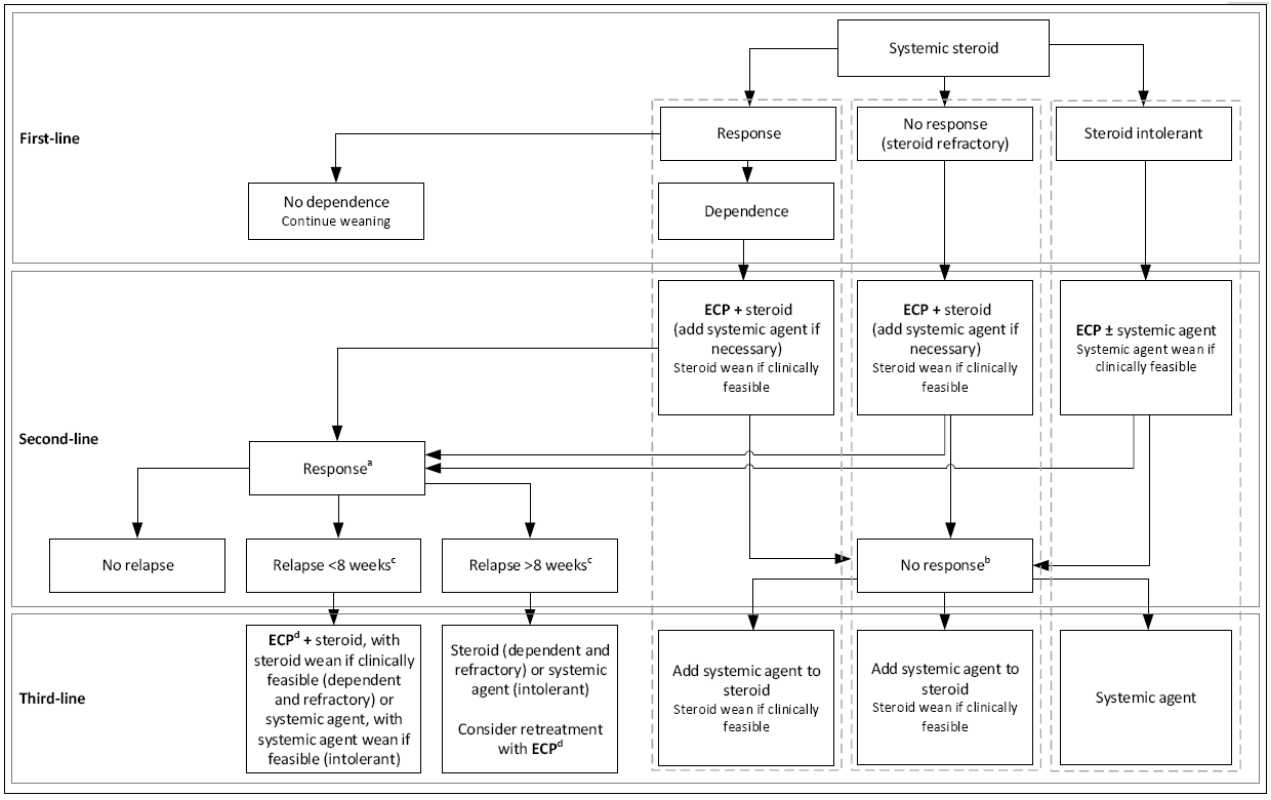
The current clinical management algorithm (MSAC Application 1651 PSD Figure 2 p12) positions ECP as a second-line therapy for cGVHD (Figure 1). First-line therapy consists of systemic corticosteroids (prednisone) initially, with tapering undertaken when appropriate. Clinicians evaluate patient response, dependence, or intolerance to corticosteroids to assess the need for second-line treatment. Patients who are steroid-refractory, steroid-dependent, or steroid-intolerant progress to second-line therapy, which includes ECP either alone or in combination with other systemic agents. The supported MBS item descriptor (MSAC Application 1651 PSD p12) defines steroid-refractory or steroid-dependent disease as one of the following:

- A lack of response or disease progression after a minimum of prednisone 1 mg/kg/day or equivalent for at least 1 week, OR
- Disease persistence without improvement despite continued treatment with prednisone at > 0.5 mg/kg/day or 1 mg/kg every day or equivalent other day for at least 4 weeks, OR

- Increase to prednisolone dose to > 0.25 mg/kg/day or equivalent after 2 unsuccessful attempts to taper the dose.

In addition, steroid-intolerance is defined as when patients who are unable to tolerate the side effects of adequate doses of systemic steroids (Das-Gupta et al. 2014).

Figure 1 Clinical management algorithm



Source: Adapted from MSAC Application 1651 Figure 2 p12

a) Response: the initial treatment cycle would be 12 weeks, then review and continue with another 12-week treatment cycle if the patient is responding. PASC noted that clinicians review the treatment every 12 weeks before continuing. PASC noted that the initial 12-week treatment cycle is twice per week, and the second 12-week cycle is twice per month. PASC noted that the definition of "response" was limited to an improvement in cGVHD symptoms. PASC advised that for the steroid-dependent population, the definition of "response" might also appropriately include a reduction in use of concomitant therapy (with a reduction of steroid dose being the most expected response)
b) No response: patients who do not respond sufficiently to ECP after the initial 12-week cycle should not continue with the treatment
c) From cessation of ECP
d) Re-using the initiation regimen for ECP (12-week treatment cycle, twice per week)

Note: For some patients starting ECP as third-line and later-line, ECP may also be added to systemic steroids and/or other treatment, with the aim of weaning both steroids and other therapy. Systemic agent options are calcineurin inhibitors (e.g. tacrolimus and ciclosporin) or mycophenolate mofetil.

Provide a rationale for the specifics of the eligible population:

The Medical Services Advisory Committee (MSAC) previously accepted the high clinical need in patients with cGVHD, and acknowledged that integrated, closed-system ECP has an established place in the clinical management algorithm as a second-line therapy (MSAC Application 1651 PSD Figure 2 p12). This application does not seek to change the eligibility criteria for ECP, but to extend the current prescriber restriction which states that the service must be provided by, or on behalf of a specialist or consultant physician who is practising in the speciality of haematology or oncology, to allow dermatologists to also supervise this service. The original restriction was informed by clinical practice at the time of the initial MSAC submission, when ECP was only available at two centres in Australia: The Peter MacCallum Cancer Centre and the Royal Prince Alfred Hospital. Both services operated within apheresis units and were primarily staffed by haematologists. Accordingly, expert consultation for the original application came predominantly from the haematology field. However, this limitation was not a central requirement of the MSAC submission, and it does not reflect current clinical practice or international standards. As such, an

extension of supervision of ECP to dermatologists would better reflect contemporary practice in Australia, where dermatologists are already involved in the management of patients with cGVHD as integral members of multidisciplinary care teams.

In other jurisdictions, dermatologists are involved in the delivery of ECP. The European Dermatology Forum published clinical guidelines in 2013, which were updated in 2020 (Knobler et al. 2020; Knobler et al. 2014). Developed through consultation both within and outside the field of dermatology, these guidelines currently represent the most comprehensive expert recommendations for the use of ECP, based on published literature and consensus opinion. In the United Kingdom (UK), ECP is formally endorsed by the UK Photopheresis Society for cGVHD. ECP services are delivered through specialised NHS centres located in regions throughout the UK. All designated centres assess and manage patients with cGVHD, with dermatologists routinely involved in both referral and longitudinal clinical care. In Germany, ECP is predominantly delivered within hospital-based settings, typically with departments of dermatology, haematology, or transfusion medicine. Access is enabled through established procedural codes, allowing dermatologists to initiate, coordinate, and oversee ECP therapy as part of multidisciplinary inpatient services. More recently in Australia, the optimal care pathway for cGVHD management emphasises the role of multidisciplinary care teams. Dermatologists are recognised as key contributors to these teams, as they are uniquely positioned to assess the characteristic skin involvement of the disease, which is common at the onset of cGVHD and occurs in approximately 75% of cases (Lee and Flowers 2008). Their established clinical experience with phototherapy and ultraviolet (UV) interventions similarly supports their capacity to supervise light-based therapies such as ECP for the management of cGVHD (Tan and GeBauer 2025).

While availability of ECP in Australia has expanded since the initial MSAC submissions, it remains limited, with services currently available at one hospital in each of New South Wales, South Australia, and Queensland, and three hospitals in Victoria. Expert clinical opinion indicates that expanding prescribing rights to dermatologists would facilitate the establishment of additional sites, improving equity of access for this small but high-need patient population. Given that MSAC has accepted that ECP has superior clinical effectiveness and non-inferior safety compared with standard of care for cGVHD (MSAC Application 1651 PSD p4), increasing access to this validated treatment – while maintaining the safety, efficacy, and cost-effectiveness parameters that MSAC has already endorsed – would represent a pragmatic and patient-centred change.

Are there any prerequisite tests?

No

Are the prerequisite tests MBS funded?

Not applicable

Provide details to fund the prerequisite tests:

Not applicable

Intervention

Name of the proposed health technology:

Integrated, closed-system, extracorporeal photopheresis (ECP)

Methoxsalen (UVADEX®)

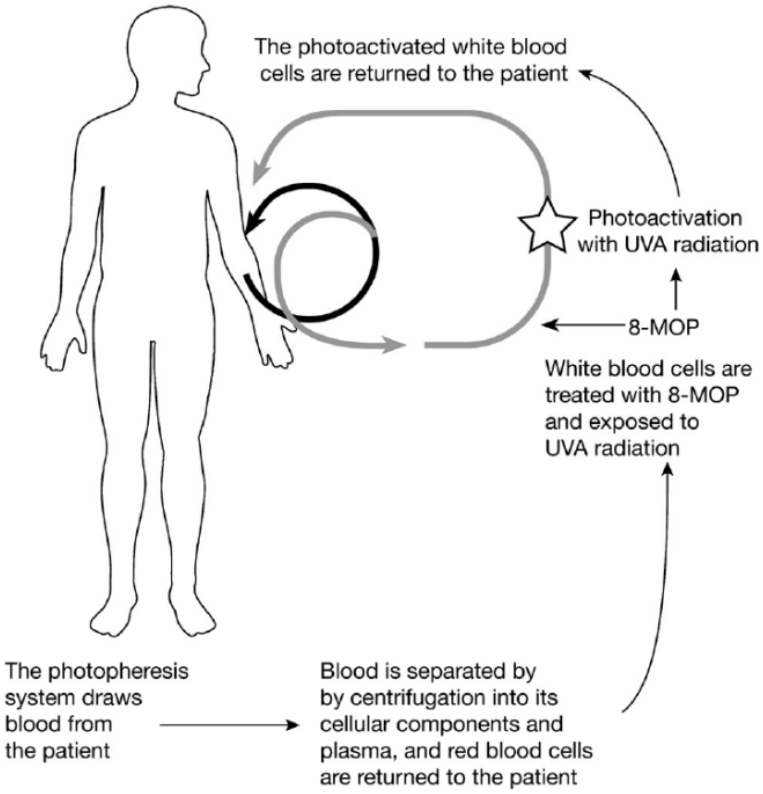
Describe the key components and clinical steps involved in delivering the proposed health technology:

Extracorporeal photopheresis

ECP is a leukapheresis-based, immunomodulatory therapy in which a patient's leukocytes are collected and treated ex-vivo with methoxsalen and UVA light and then returned to the patient (Figure 2). Integrated, closed ECP systems complete the processes of cell separation, photo activation of

methoxsalen (UVADEX®), and reinfusion of the treated cells back into the patient within an automated and fully integrated process (Knobler et al. 2014). All components of the treatment are validated for use together. Treatment of cGVHD with integrated ECP systems is well established (Asensi Cantó et al. 2023), and endorsed by international clinical guidelines (Knobler et al. 2020; Knobler et al. 2014; Penack et al. 2020).

Figure 2 Overview of ECP



Abbreviations: 8-MOP, methoxsalen; UVA, ultraviolet A
Note: Blood is removed from the patient, and the red blood cells (RBC) and white blood cells (WBC) are separated. RBC are immediately returned to the patient, whereas WBC are treated with methoxsalen (8-MOP) and ultraviolet A (UVA) radiation to photoactivate the drug; photoactivated WBC are then returned to the patient.
Source: Worel and Leitner (2012)

Photopheresis is also performed with open systems, also known as two-step methods, which are characterised by different devices for cell separation and drug photo activation (Knobler et al. 2014). In these systems the combination of the device for separation and the device for photoactivation has not been approved for use together or specifically approved for photopheresis (Knobler et al. 2014). The two-step approach also increases the potential risk of patient reinfusion error, infection and cross-contamination (Knobler et al. 2014). Open systems are only recommended for use in centres that have approval for handling blood components separately (Knobler et al. 2014). MSAC has not assessed the efficacy or cost-effectiveness of open systems for the treatment of cGVHD.

Methoxsalen

Methoxsalen is a naturally occurring photoactive substance found in the seeds of the Ammi majus (Umbelliferae) plant and in the roots of Heracleum Candicans. It belongs to a group of compounds known as psoralens, or furocoumarins. Methoxsalen is pharmacologically active only when exposed to ultraviolet light in the UVA range (320 to 400 nm).

The ECP procedure involves chemical treatment of WBC with a drug that is activated by light (e.g. methoxsalen), exposing this mix to ultraviolet light and returned to the patient. The reinfused leukocytes, now damaged by methoxsalen plus UVA, trigger downstream immunologic effects: inducing tolerogenic antigen-presenting cell behaviour, skewing immune regulation (e.g., promoting regulatory T cells), reducing pathogenic donor T cell responses, and modulating B-cell and monocyte/macrophage

contributions to cGVHD which attenuates the effect immune response against the host tissue (Asensi Cantó et al. 2023).

Identify how the proposed technology achieves the intended patient outcomes:

ECP is used in combination with PBS reimbursed methoxsalen to treat patients with cGVHD. MSAC has previously accepted that ECP plus methoxsalen has acceptable safety, superior effectiveness and acceptable cost-effectiveness in the treatment of cGVHD compared with the current standard of care alone for the proposed patient population. MSAC also advised that there was a high unmet clinical need for effective treatments for cGVHD, given that it is not well managed by existing therapies (MSAC Application 1651 PSD).

cGVHD is a debilitating, long-term, and often fatal immunological condition which occurs in approximately 50% of patients who undertake allogeneic HSCT in Australia (ABMTRR 2019). In cGVHD, a complex interaction between donor and recipient adaptive immunity occurs, causing the patient's activated donor T cells to attack their own tissues as antigenic differences cause the immune response to recognise host tissues as antigenically foreign. This immune response causes extensive tissue damage, with the most commonly involved organs including the liver, skin, mucosa, and the gastrointestinal tract (Ferrara et al. 2009; Welniak et al. 2007). As a result, the non-relapse mortality rate for patients with cGVHD who do not respond to first-line treatment is ~30% over 5 years (Martin et al. 2017).

The first-line treatment for cGVHD consists of corticosteroids which are used to suppress the immune system, including aberrant immunological processes which cause systemic organ damage. However, ~40% of cGVHD patients will fail to respond adequately to first-line treatment and will experience through one of three pathways (Lee and Zeiser 2025):

- unmanageable toxicity to corticosteroid medication (steroid-intolerant); or
- dependency on high dosages of corticosteroids without the ability to taper (steroid-dependent); or
- fail to respond to steroid medication at any dosage (steroid-refractory).

ECP combined with methoxsalen significantly improves clinical outcomes in patients with treatment-refractory cGVHD compared with standard care. Evidence presented to support the MSAC submission from multiple studies, including the pivotal randomised controlled trial by Flowers et al. (2008) and Australian Special Access Scheme (SAS) studies conducted at the Royal Prince Alfred Hospital and the Victorian Comprehensive Cancer Centre demonstrated ECP was associated with no treatment-related deaths and very few discontinuations due to adverse events, confirming its long-term tolerability.

The Flowers et al. (2008) randomised controlled trial demonstrated markedly higher rates of complete or partial response in both skin (40% vs 10%, $p < 0.01$) and extracutaneous organs including eyes (30% vs 7%) and mouth (53% vs 27%) following 12 weeks of ECP treatment. Consistent results were observed in the Australian RPAH SAS study, where 79% of patients achieved a clinical response, and in the VCCC SAS study which reported overall response rates of 82% in adults and 77% in paediatric patients.

ECP also produced meaningful systemic benefits, including significant reductions in corticosteroid and immunosuppressant use. In Flowers et al. (2008) 20.8% of patients achieved a ≥50% reduction in steroid dose versus 6.4% under standard care, these findings were supported by a number of studies (Dignan et al. 2014; Foss et al. 2005; Gandelman et al. 2018; Okamoto et al. 2018; Seaton et al. 2003). These reductions in medication burden are clinically important, decreasing long-term toxicity risks from chronic immunosuppression. The MSAC considered that reducing or substituting long-term steroids and immunosuppressant medication was also an important outcome for alleviating their cumulative adverse effects for patients and considered that this long-term consequence would not be captured in the short-term evidence presented in the applicant-developed assessment report (ADAR) (MSAC Application 1651 PSD).

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

Yes

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

Both methoxsalen and the photopheresis system are registered components. Methoxsalen (ARTG 38832) was approved for listing on the ARTG in September 2019 for the following therapeutic use:

'*Uvadex (methoxsalen) is indicated for extracorporeal administration with the Therakos Cellex Photopheresis System for the treatment of steroid-refractory and steroid-intolerant chronic graft-versus-host disease (cGVHD) in adults following allogeneic haematopoietic stem cell (HSC) transplantation*'.

As such methoxsalen is only indicated for use with the THERAKOS® CELLEX® Photopheresis System Instrument systems. Therefore, substituting this system with another component or device would not align with the ARTG-approved indication. Alternative components have not been evaluated or approved for use with methoxsalen in this context.

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):

Yes

Provide details and explain:

This submission proposes no changes to the dosage, quantity, duration, or frequency of ECP administration compared with MSAC's previous consideration. The safety, efficacy, and cost-effectiveness parameters endorsed by MSAC in 2021 remain unchanged (MSAC Application 1651 PSD).

The application seeks to extend the current prescriber restriction, which currently requires that the service be supervised by a specialist or consultant physician in the specialty of haematology or oncology, to also allow dermatologists to supervise the service.

As previously described, this change will address existing accessibility barriers impacting access to ECP services as ECP services in Australia remain limited to a small number of hospital sites. Allowing dermatologists to supervise the service will facilitate the establishment of additional treatment centres, improving geographical accessibility and equity of access for this small but high-need patient population.

If applicable, advise which health professionals will be needed to provide the proposed health technology:

The current MBS items for ECP for the treatment of cGVHD, items 13761 and 13762, state that the service must be provided by, or on behalf of, a specialist or consultant physician who: (i) is practising in the speciality of haematology or oncology; and (ii) has experience with allogeneic bone marrow transplantation. This is consistent with the PBS restriction for methoxsalen for the treatment of cGVHD 12839R, 12854M, 12855N, 12876Q which contain treatment criteria which states that the patient must be treated by a haematologist, or, must be treated by an oncologist with allogeneic bone marrow transplantation experience; or, must be treated by a medical practitioner working under the direct supervision of one of the above mentioned specialist types. This application seeks to extend the current treatment restrictions to include dermatologists reflecting contemporary multidisciplinary practice in the management of cGVHD

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

ECP delivery requires a multidisciplinary clinical team to support the management of patients with cGVHD. This team may include dermatologists, oncologists, haematologists, specialist nurses, apheresis technicians, and transfusion medicine staff. Haematologists, oncologists, and dermatologists are responsible for clinical oversight and patient management, while trained nursing and technical staff perform the photopheresis procedure and monitor treatment safety.

This application proposes that the current restriction on specialist supervision be expanded to also allow supervision by dermatologists, reflecting contemporary multidisciplinary practice and improving accessibility to ECP services.

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

Not applicable

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?

No

Provide details and explain:

Not applicable

Indicate the proposed setting(s) in which the proposed health technology will be delivered:

- ☐ Consulting rooms
- ☐ Day surgery centre
- ☐ Emergency Department
- ☒ Inpatient private hospital
- ☒ Inpatient public hospital
- ☐ Laboratory
- ☐ Outpatient clinic
- ☐ Patient's home
- ☐ Point of care testing
- ☐ Residential aged care facility
- ☐ Other (please specify)

Is the proposed health technology intended to be entirely rendered inside Australia?

Yes

Provide additional details on the proposed health technology to be rendered outside of Australia:

Not applicable

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e., how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian healthcare system). This includes identifying healthcare resources that are needed to be delivered at the same time as the comparator service:

Not applicable

List any existing MBS item numbers that are relevant for the nominated comparators:

Not applicable

Provide a rationale for why this is a comparator:

Not applicable

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

- ☐ None (used with the comparator)
- ☐ Displaced (comparator will likely be used following the proposed technology in some patients)
- ☐ Partial (in some cases, the proposed technology will replace the use of the comparator, but not all)
- ☐ Full (subjects who receive the proposed intervention will not receive the comparator)

Outline and explain the extent to which the current comparator is expected to be substituted:

Not applicable

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☒ Health harms
☐ Resources
☐ Value of knowing

Outcome description – include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

The MSAC has accepted that ECP plus methoxsalen has acceptable safety, superior effectiveness and acceptable cost-effectiveness in the treatment of cGVHD compared with the current standard of care alone for the treatment of cGVHD for patients who are steroid-dependent and/or steroid-intolerant and/or steroid-refractory (MSAC Application 1651 PSD).

The outcomes assessed by MSAC in the July 2021 submission were:

a) Total skin score
b) Response rate in cutaneous and extracutaneous affected organs
c) Reductions in immunosuppressant medications
d) Safety

This submission requests that the current restriction for supervision of ECP be expanded to include dermatologists, in addition to haematologists. This proposed change is not expected to alter the clinical outcomes previously accepted by MSAC, as it does not modify the treatment indication, delivery method, dosage, or duration of therapy.

Proposed MBS items

How is the technology/service funded at present? (e.g., research funding; State-based funding; self-funded by patients; no funding or payments):

In July 2021, MSAC supported an application for public funding of extracorporeal photopheresis (ECP) for chronic graft-versus-host disease (cGVHD) by the MBS. The service is currently funded on the MBS under items 13761 and 13762. Methoxsalen is reimbursed on the PBS under items 12154Q, 12156T, 12162D, and 12173Q.

Provide at least one proposed item with their descriptor and associated costs, for each Population/Intervention:

MBS item number (where used as a template for the proposed item)	**13761**
Category number	3
Category description	Therapeutic procedures
Proposed item descriptor	Extracorporeal photopheresis for the treatment of chronic graft-versus-host disease, if: (a) the person is: i. has received allogeneic haematopoietic stem cell transplantation; and ii. has been diagnosed with chronic graft-versus-host disease following the transplantation; and iii. steroid treatment is clinically unsuitable as the disease is steroid-refractory or the person is steroid-dependent or steroid-intolerant; and (b) the person has not previously received extracorporeal photopheresis treatment; and (c) the service is delivered using an integrated, closed extracorporeal photopheresis system; and (d) the service is provided in combination with the use of methoxsalen that is listed on the Pharmaceutical Benefits Scheme; and (e) the service is provided by, or on behalf of, a specialist or consultant physician who: i. is practising in the speciality of haematology or oncology ***or dermatology; and*** ii. has experience with allogeneic bone marrow transplantation. Applicable once per treatment session (H)
Proposed MBS fee	Fee: $2,139.55 Benefit: 75% = $1,604.70
Indicate the overall cost per patient of providing the proposed health technology	$2,139.55
Please specify any anticipated out of pocket expenses	No additional out of pocket costs are expected
Provide any further details and explain	The application does not propose any change to the MBS fee for ECP services for cGVHD

MBS item number (where used as a template for the proposed item)	**13762**
Category number	3
Category description	Therapeutic procedures
Proposed item descriptor	Extracorporeal photopheresis for the treatment of chronic graft-versus-host disease, if: (a) the person is: i. has received allogeneic haematopoietic stem cell transplantation; and ii. has been diagnosed with chronic graft-versus-host disease following the transplantation; and iii. steroid treatment is clinically unsuitable as the disease is steroid-refractory or the person is steroid-dependent or steroid-intolerant; and (b) the person has previously received an extracorporeal photopheresis treatment cycle and had a partial or complete response in at least one organ in response to treatment; and (c) the person requires further extracorporeal photopheresis; and (d) the service is delivered using an integrated, closed extracorporeal photopheresis system; and (e) the service is provided in combination with the use of methoxsalen that is listed on the Pharmaceutical Benefits Scheme; and (f) the service is provided by, or on behalf of, a specialist or consultant physician who: iii. is practising in the speciality of haematology or oncology ***or dermatology; and*** iv. has experience with allogeneic bone marrow transplantation. Applicable once per treatment session (H)
Proposed MBS fee	Fee: $2,139.55 Benefit: 75% = $1,604.70
Indicate the overall cost per patient of providing the proposed health technology	$2,139.55
Please specify any anticipated out of pocket expenses	No additional out of pocket costs are expected
Provide any further details and explain	The application does not propose any change to the MBS fee for ECP services for cGVHD

Algorithms

PREPARATION FOR USING THE HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

The current clinical management algorithm (MSAC Application 1651 PSD Figure 2 p12) positions ECP as a second-line therapy for cGVHD (Figure 3). First-line therapy consists of systemic corticosteroids (prednisone) initially, with tapering undertaken when appropriate. Clinicians evaluate patient response, dependence, or intolerance to corticosteroids to assess the need for second-line treatment. Patients who are steroid-refractory, steroid-dependent, or steroid-intolerant progress to second-line therapy, which includes ECP either alone or in combination with other systemic agents. The supported MBS item

descriptor (MSAC Application 1651 PSD p12) defines steroid-refractory or steroid-dependent disease as one of the following:

- A lack of response or disease progression after a minimum of prednisone 1 mg/kg/day or equivalent for at least 1 week, OR
- Disease persistence without improvement despite continued treatment with prednisone at > 0.5 mg/kg/day or 1 mg/kg every day or equivalent other day for at least 4 weeks, OR
- Increase to prednisolone dose to > 0.25 mg/kg/day or equivalent after 2 unsuccessful attempts to taper the dose.

In addition, steroid-intolerance is defined as when patients who are unable to tolerate the side effects of adequate doses of systemic steroids (Das-Gupta et al. 2014).

Is there any expectation that the clinical management algorithm before the health technology is used will change due to the introduction of the proposed health technology?

No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

Not applicable

USE OF THE HEALTH TECHNOLOGY

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

Methoxsalen (UVADEX®)

Explain what other healthcare resources are used in conjunction with the comparator health technology:

Not applicable

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

Not applicable

CLINICAL MANAGEMENT AFTER THE USE OF HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the proposed health technology:

The clinical management algorithm will remain unchanged as ECP is currently funded cGVHD via MBS items 13761 and 13762. As such, healthcare resourcing costs are expected to remain consistent with current practice. After the use of ECP in the algorithm (if an individual has refractory disease progress), they will progress to third-line treatment (Figure 3).

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the comparator health technology:

Not applicable

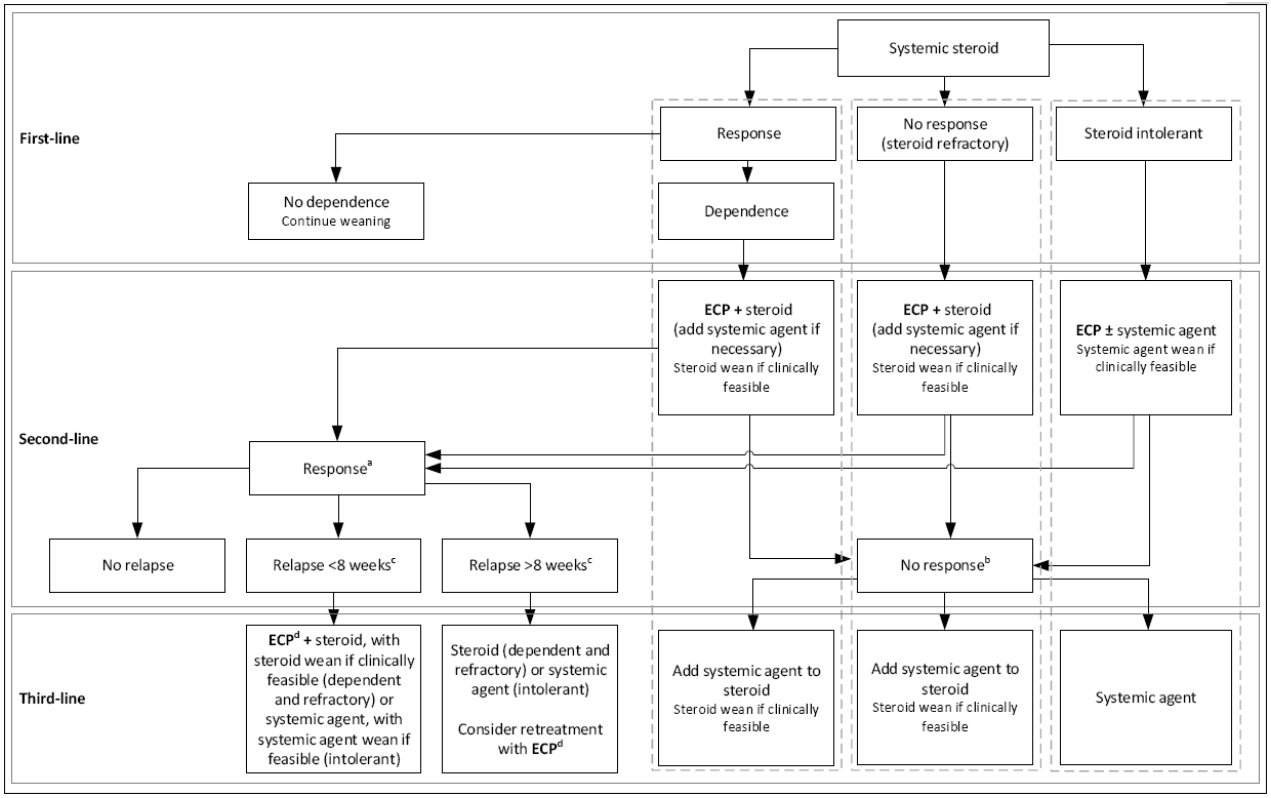
Describe and explain any differences in the healthcare resources used after the proposed health technology vs. the comparator health technology:

Not applicable; no differences.

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Figure 3 demonstrates the current clinical management algorithm, which already uses extracorporeal photopheresis; no change is being sought here.

Figure 3 Clinical management algorithm



Source: Adapted from MSAC Application 1651 Figure 2 p12

a) Response: the initial treatment cycle would be 12 weeks, then review and continue with another 12-week treatment cycle if the patient is responding. PASC noted that clinicians review the treatment every 12 weeks before continuing. PASC noted that the initial 12-week treatment cycle is twice per week, and the second 12-week cycle is twice per month. PASC noted that the definition of "response" was limited to an improvement in cGVHD symptoms. PASC advised that for the steroid-dependent population, the definition of "response" might also appropriately include a reduction in use of concomitant therapy (with a reduction of steroid dose being the most expected response)
b) No response: patients who do not respond sufficiently to ECP after the initial 12-week cycle should not continue with the treatment
c) From cessation of ECP
d) Re-using the initiation regimen for ECP (12-week treatment cycle, twice per week)

Note: For some patients starting ECP as third-line and later-line, ECP may also be added to systemic steroids and/or other treatment, with the aim of weaning both steroids and other therapy. Systemic agent options are calcineurin inhibitors (e.g. tacrolimus and ciclosporin) or mycophenolate mofetil.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

☐ Superior
☒ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:

The clinical claim is unchanged from the July 2021 submission. MSAC considered that ECP plus methoxsalen has acceptable safety, superior effectiveness and acceptable cost-effectiveness in the treatment of cGVHD compared with the current standard of care alone for the proposed patient population. Expanding treatment criteria for the service to allow supervision by dermatologists is not expected to affect this claim.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

Not applicable

Identify how the proposed technology achieves the intended patient outcomes:

ECP is used in combination with PBS reimbursed methoxsalen to treat patients with cGVHD. MSAC has previously accepted that ECP plus methoxsalen has acceptable safety, superior effectiveness and acceptable cost-effectiveness in the treatment of cGVHD compared with the current standard of care alone for the proposed patient population. MSAC also advised that there was a high unmet clinical need for effective treatments for cGVHD, given that it is not well managed by existing therapies (MSAC application 1651 PSD).

cGVHD is a debilitating, long-term, and often fatal immunological condition which occurs in approximately 50% of patients who undertake allogenic HSCT in Australia (ABMTRR 2019). In cGVHD, a complex interaction between donor and recipient adaptive immunity occurs, causing the patient's activated donor T cells to attack their own tissues as antigenic differences cause the immune response to recognise host tissues as antigenically foreign. This immune response causes extensive tissue damage, with the most commonly involved organs including the liver, skin, mucosa, and the gastrointestinal tract (Ferrara et al. 2009; Welniak et al. 2007). As a result, the non-relapse mortality rate for patients with cGVHD who do not respond to first-line treatment is ~30% over 5 years (Martin et al. 2017).

The first-line treatment for cGVHD consists of corticosteroids which are used to suppress the immune system, including aberrant immunological processes which cause systemic organ damage. However, ~40% of cGVHD patients will fail to respond adequately to first-line treatment and will experience through one of three pathways (Lee and Zeiser 2025):

- unmanageable toxicity to corticosteroid medication (steroid-intolerant); or
- dependency on high dosages of corticosteroids without the ability to taper (steroid-dependent); or
- fail to respond to steroid medication at any dosage (steroid-refractory).

ECP combined with methoxsalen significantly improves clinical outcomes in patients with treatment-refractory cGVHD compared with standard care. Evidence presented to support the MSAC submission from multiple studies, including the pivotal randomised controlled trial by Flowers et al. (2008) and Australian SAS studies conducted at the Royal Prince Alfred Hospital and the Victorian Comprehensive Cancer Centre demonstrated ECP was associated with no treatment-related deaths and very few discontinuations due to adverse events, confirming its long-term tolerability.

The Flowers et al. (2008) randomised controlled trial demonstrated markedly higher rates of complete or partial response in both skin (40% vs 10%, $p < 0.01$) and extracutaneous organs including eyes (30% vs 7%) and mouth (53% vs 27%) following 12 weeks of ECP treatment. Consistent results were observed in the Australian RPAH SAS study, where 79% of patients achieved a clinical response, and in the VCCC SAS study which reported overall response rates of 82% in adults and 77% in paediatric patients.

ECP also produced meaningful systemic benefits, including significant reductions in corticosteroid and immunosuppressant use. In Flowers et al. (2008) 20.8% of patients achieved a ≥50% reduction in steroid dose versus 6.4% under standard care, these findings were supported by a number of studies (Dignan et al. 2014; Foss et al. 2005; Gandelman et al. 2018; Okamoto et al. 2018; Seaton et al. 2003). These reductions in medication burden are clinically important, decreasing long-term toxicity risks from chronic immunosuppression. MSAC considered that reducing or substituting long-term steroids and immunosuppressant medication was also an important outcome for alleviating their cumulative adverse effects for patients and considered that this long-term consequence would not be captured in the short-term evidence presented in the ADAR (MSAC application 1651 PSD).

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management?

Not applicable

A change in health outcome?

Not applicable

Other benefits?

Not applicable

Please provide a rationale, and information on other benefits if relevant:

Not applicable

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?

☐ More costly
☒ Same cost
☐ Less costly

Provide a brief rationale for the claim:

This submission proposes no change to cost of ECP or methoxsalen. Cost-effectiveness is expected to be consistent with what was previously accepted by MSAC in 2021 (MSAC application 1651 PSD).

If your application is in relation to a specific radiopharmaceutical(s) or a set of radiopharmaceuticals, identify whether your clinical claim is dependent on the evidence base of the radiopharmaceutical(s) for which MBS funding is being requested. If your clinical claim is dependent on the evidence base of another radiopharmaceutical product(s), a claim of clinical noninferiority between the radiopharmaceutical products is also required.

Not applicable

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement'

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	Guideline	Updated guidelines on the use of extracorporeal photopheresis 2020 Updated Guidelines on the Use of Extracorporeal Photopheresis 2020	European Dermatology Forum (EDF) guidelines on the use of extracorporeal photopheresis across multiple conditions. Outlines mechanisms, protocols, treatment, assessments, safety data, and expert clinical opinion.	Part 1: https://pubmed.ncbi.nlm.nih.gov/33025659/ Part 2: https://pubmed.ncbi.nlm.nih.gov/32964529/	2020 (update to 2014 version)
2.	Guideline	Guidelines on the use of extracorporeal photopheresis	Precursor to 2020 guideline (above). Recommendations and guidelines on extracorporeal photopheresis use across multiple conditions, with clinical data reviewed up to 2014.	https://pubmed.ncbi.nlm.nih.gov/24354653/	2014
3.	Guideline	Guidelines for phototherapy and PUVA service delivery in Australia: Minimum standards and quality assurance framework	Australian dermatology guideline establishing national framework and minimum standards for phototherapy and psoralen plus ultraviolet A radiation (PUVA) therapy. Spans management process for treatment and training for clinicians.	https://pubmed.ncbi.nlm.nih.gov/40762446/	2025

REFERENCES

ABMTRR (2019). Australasian Bone Marrow Transplant Recipient Registry Annual Data Summary 2018. Australasian Bone Marrow Transplant Recipient Registry.

Asensi Cantó P, J Sanz Caballer, P Solves Alcaína, J de la Rubia Comos and I Gómez Seguí (2023). Extracorporeal Photopheresis in Graft-versus-Host Disease. *Transplantation and Cellular Therapy* 29(9): 556-566.

Berger M, R Albiani, B Sini and F Fagioli (2015). Extracorporeal photopheresis for graft-versus-host disease: the role of patient, transplant, and classification criteria and hematologic values on outcome-results from a large single-center study. *Transfusion* 55(4): 736-747.

Das-Gupta E, F Dignan, B Shaw, K Raj, R Malladi, A Gennery, D Bonney, P Taylor and J Scarisbrick (2014). Extracorporeal photopheresis for treatment of adults and children with acute GVHD: UK consensus statement and review of published literature. *Bone Marrow Transplant* 49(10): 1251-1258.

Dignan FL, S Aguilar, JJ Scarisbrick, BE Shaw, MN Potter, J Cavenagh, JF Apperley, AK Fielding, A Pagliuca, K Raj, DI Marks, A Peniket, C Crawley, MB Koh and FJ Child (2014). Impact of extracorporeal photopheresis on skin scores and quality of life in patients with steroid-refractory chronic GVHD. *Bone Marrow Transplant* 49(5): 704-708.

Ferrara JL, JE Levine, P Reddy and E Holler (2009). Graft-versus-host disease. *Lancet* 373(9674): 1550-1561.

Flowers ME, JF Apperley, K van Besien, A Elmaagacli, A Grigg, V Reddy, A Bacigalupo, HJ Kolb, L Bouzas, M Michallet, HM Prince, R Knobler, D Parenti, J Gallo and HT Greinix (2008). A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. *Blood* 112(7): 2667-2674.

Foss FM, GM DiVenuti, K Chin, K Sprague, H Grodman, A Klein, G Chan, K Stiffler and KB Miller (2005). Prospective study of extracorporeal photopheresis in steroid-refractory or steroid-resistant extensive chronic graft-versus-host disease: analysis of response and survival incorporating prognostic factors. *Bone Marrow Transplant* 35(12): 1187-1193.

Gandelman JS, DJ Song, H Chen, BG Engelhardt, YB Chen, WB Clark, CR Giver, EK Waller, DK Jung and M Jagasia (2018). A Prospective Trial of Extracorporeal Photopheresis for Chronic Graft-versus-Host Disease Reveals Significant Disease Response and No Association with Frequency of Regulatory T Cells. *Biol Blood Marrow Transplant* 24(12): 2373-2380.

Jagasia MH, HT Greinix, M Arora, KM Williams, D Wolff, EW Cowen, J Palmer, D Weisdorf, NS Treister, GS Cheng, H Kerr, P Stratton, RF Duarte, GB McDonald, Y Inamoto, A Vigorito, S Arai, MB Datiles, D Jacobsohn, T Heller, CL Kitko, SA Mitchell, PJ Martin, H Shulman, RS Wu, CS Cutler, GB Vogelsang, SJ Lee, SZ Pavletic and ME Flowers (2015). National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant* 21(3): 389-401 e381.

Knobler R, P Arenberger, A Arun, C Assaf, M Bagot, G Berlin, A Bohbot, P Calzavara-Pinton, F Child, A Cho, LE French, AR Gennery, R Gniadecki, HPM Gollnick, E Guenova, P Jaksch, C Jantschitsch, C Klemke, J Ludvigsson, E Papadavid, J Scarisbrick, T Schwarz, R Stadler, P Wolf, J Zic, C Zouboulis, A Zuckermann and H Greinix (2020). European dermatology forum - updated guidelines on the use of extracorporeal photopheresis 2020 - part 1. *J Eur Acad Dermatol Venereol* 34(12): 2693-2716.

Knobler R, G Berlin, P Calzavara-Pinton, H Greinix, P Jaksch, L Laroche, J Ludvigsson, P Quaglino, W Reinisch, J Scarisbrick, T Schwarz, P Wolf, P Arenberger, C Assaf, M Bagot, M Barr, A Bohbot, L Bruckner-Tuderman, B Dreno, A Enk, L French, R Gniadecki, H Gollnick, M Hertl, C Jantschitsch, A Jung, U Just, CD Klemke, U Lippert, T Luger, E Papadavid, H Pehamberger, A Ranki, R Stadler, W Sterry, IH Wolf, M Worm,

J Zic, CC Zouboulis and U Hillen (2014). Guidelines on the use of extracorporeal photopheresis. *J Eur Acad Dermatol Venereol* 28 Suppl 1(Suppl 1): 1-37.

Lee SJ (2017). Classification systems for chronic graft-versus-host disease. *Blood* 129(1): 30-37.

Lee SJ and ME Flowers (2008). Recognizing and managing chronic graft-versus-host disease. *Hematology Am Soc Hematol Educ Program*: 134-141.

Lee SJ and R Zeiser (2025). FDA-approved therapies for chronic GVHD. *Blood* 145(8): 795-800.

Martin PJ, BE Storer, Y Inamoto, MED Flowers, PA Carpenter, J Pidala, J Palmer, M Arora, M Jagasia, S Arai, CS Cutler and SJ Lee (2017). An endpoint associated with clinical benefit after initial treatment of chronic graft-versus-host disease. *Blood* 130(3): 360-367.

MSAC (2021). Public Summary Document: Application No. 1651 – Integrated, closed-system, extracorporeal photopheresis systems for the treatment of chronic graft-versus-host disease. Medical Services Advisory Committee, Australian Government.

Okamoto S, T Teshima, M Kosugi-Kanaya, K Kahata, N Kawashima, J Kato, T Mori, Y Ozawa and K Miyamura (2018). Extracorporeal photopheresis with TC-V in Japanese patients with steroid-resistant chronic graft-versus-host disease. *Int J Hematol* 108(3): 298-305.

Penack O, M Marchetti, T Ruutu, M Aljurf, A Bacigalupo, F Bonifazi, F Ciceri, J Cornelissen, R Malladi, RF Duarte, S Giebel, H Greinix, E Holler, A Lawitschka, S Mielke, M Mohty, M Arat, A Nagler, J Passweg, H Schoemans, G Socié, C Solano, R Vrhovac, R Zeiser, N Kröger and GW Basak (2020). Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. *The Lancet Haematology* 7(2): e157-e167.

Seaton ED, RM Szydlo, E Kanfer, JF Apperley and R Russell-Jones (2003). Influence of extracorporeal photopheresis on clinical and laboratory parameters in chronic graft-versus-host disease and analysis of predictors of response. *Blood* 102(4): 1217-1223.

Tan S and K GeBauer (2025). Guidelines for Phototherapy and PUVA Service Delivery in Australia: Minimum Standards and Quality Assurance Framework. *Australas J Dermatol*.

van der Wagen L, L Te Boome, M Schiffler, I Nijhof, M Schoordijk, S van Dorp, M van Dijk, R Raymakers, E Petersen, M de Witte, N de Jong, M Bellido, B Bar, E Meijer and J Kuball (2018). Prospective evaluation of sequential treatment of sclerotic chronic graft versus host disease with rituximab and nilotinib. *Bone Marrow Transplant* 53(10): 1255-1262.

Welniak LA, BR Blazar and WJ Murphy (2007). Immunobiology of allogeneic hematopoietic stem cell transplantation. *Annu Rev Immunol* 25: 139-170.

Wood WA, X Chai, D Weisdorf, PJ Martin, C Cutler, Y Inamoto, D Wolff, SZ Pavletic, J Pidala, JM Palmer, M Arora, S Arai, M Jagasia, B Storer, SJ Lee and S Mitchell (2013). Comorbidity burden in patients with chronic GVHD. *Bone Marrow Transplant* 48(11): 1429-1436.

Worel N and G Leitner (2012). Clinical Results of Extracorporeal Photopheresis. *Transfus Med Hemother* 39(4): 254-262.

APPENDIX A

Table A: Signs and symptoms of chronic GVHD as per NCCN guidelines and NIH consensus (2015)

Signs and symptoms of chronic GVHD				
Organ Site	**Diagnostic (sufficient to establish the diagnosis of chronic GVHD)**	**Distinctive[a] (seen in chronic GVHD, but insufficient to establish a diagnosis)**	**Other features for unclassified entities[b]**	**Common[c] (seen with both acute and chronic GVHD)**
Skin	• Poikiloderma • Lichen planus-like features • Sclerotic features • Morphea-like features • Lichen sclerosis-like features	• Depigmentation • Papulo-squamous lesions	• Sweat impairment • Ichthyosis • Keratosis pilaris • Hypopigmentation • Hyperpigmentation	• Erythema • Maculopapular rash • Pruritus
Nails		• Dystrophy • Longitudinal ridging, splitting or brittle features • Onycholysis • Pterygium unguis • Nail loss (usually symmetric, affects most nails)		
Scalp and Body Hair		• New onset of scarring or non-scarring scalp alopecia (after recovery from chemoradiotherapy) • Loss of body hair • Scaling	• Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes) • Premature grey hair	
Mouth	• Lichen planus-like changes	• Xerostomia • Mucoceles • Mucosal atrophy • Ulcers • Pseudo-membranes		• Gingivitis • Mucositis • Erythema • Pain

Signs and symptoms of chronic GVHD				
Organ Site	**Diagnostic (sufficient to establish the diagnosis of chronic GVHD)**	**Distinctive[a] (seen in chronic GVHD, but insufficient to establish a diagnosis)**	**Other features for unclassified entities[b]**	**Common[c] (seen with both acute and chronic GVHD)**
Eyes		• New onset dry, gritty, or painful eyes • Cicatricial conjunctivitis • Keratoconjunctivitis sicca • Confluent areas of punctate keratopathy	• Photophobia • Periorbital hyperpigmentation • Blepharitis (erythema of the eye lids with oedema)	
Genitalia	• Lichen planus-like features • Lichen sclerosis-like features • Vaginal scarring or clitoral/labial agglutination (females) • Phimosis or urethral/meatus scarring or stenosis (males)	• Erosions • Fissures • Ulcers		
GI Tract	• Oesophageal web • Strictures or stenosis in the upper to mid third of the oesophagus		• Exocrine pancreatic insufficiency	• Anorexia • Nausea • Vomiting • Diarrhoea • Weight loss • Failure to thrive (infants and children)
Liver				• Total bilirubin, alkaline phosphatase • ALT >2x upper limit of normal
Lung	• Bronchiolitis obliterans diagnosed with lung biopsy • Bronchiolitis obliterans syndrome (BOS[d])	Air trapping and bronchiectasis on chest computed tomographic (CT) scan	• Cryptogenic organizing pneumonia (COP) • Restrictive lung disease[e]	

Signs and symptoms of chronic GVHD				
Organ Site	**Diagnostic (sufficient to establish the diagnosis of chronic GVHD)**	**Distinctive[a] (seen in chronic GVHD, but insufficient to establish a diagnosis)**	**Other features for unclassified entities[b]**	**Common[c] (seen with both acute and chronic GVHD)**
Muscles, Fascia, Joints	• Fasciitis • Joint stiffness or contractures secondary to fasciitis or sclerosis	• Myositis or polymyositis[f]	• Oedema • Muscle cramps • Arthralgia or arthritis	
Haematopoietic and Immune			• Thrombocytopenia • Eosinophilia • Lymphopenia • Hypo- or hyper-gammaglobulinemia • Autoantibodies (AIHA, ITP) • Raynaud's phenomenon	
Other			• Pericardia or pleural effusions • Ascites • Peripheral neuropathy • Nephrotic syndrome • Myasthenia gravis • Cardiac conduction abnormality or cardiomyopathy	

Source: Table adapted from Table 1 Jagasia et al. (2015)

a) In all cases, infection, drug effect, malignancy, or other causes must be excluded.
b) Can be acknowledged as part of the chronic GVHD manifestations diagnosis is confirmed.
c) Common refers to shared features by both acute and chronic GVHD.
d) BOS can be diagnostic for lung chronic GVHD only if distinctive signs or symptoms of chronic GVHD are present in another organ. BOS diagnosis requires the following criteria:
    1. FEV1N C ratio < 0.7 or the fifth percentile predicted.
    2. FEV1 < 75% of predicted with 10% decline within 2 years. FEV1 should not be corrected to >75% of predicted after albuterol inhalation, and the absolute decline for the corrected values should remain at 10% over 2 years.
    3. Absence of infection in the respiratory tract, documented with investigations directed by clinical symptoms, such as chest radiographs, CT scans, or microbiologic cultures (sinus aspiration, upper respiratory tract viral screen, sputum culture, bronchoalveolar lavage).
    4. One of the 2 supporting features of BOS: Evidence of air trapping by expiratory CT or small airway thickening or bronchiectasis by high resolution chest CT; or evidence of air trapping by PFTs: residual volume > 120% of predicted or residual volume/total lung capacity elevated outside the 90% confidence interval. If a patient already carries the diagnosis of chronic GVHD by virtue of organ involvement elsewhere, then only the first 3 criteria above are necessary to document chronic GVHD lung involvement.
e) Pulmonary entities under investigation or unclassified.
f) Diagnosis of chronic GVHD requires biopsy.