

MSAC APPLICATION 1732.1 IMLIFIDASE PICO SET

Population

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

The reader is referred to the Ratified PICO Confirmation and the MSAC Public Summary Document, both posted on the MSAC website under application 1732, for a more detailed description of the population.

The Australian Therapeutic Goods Administration (TGA) has approved (10/7/23) imlifidase with the tradename Idefix® for the following indication: Idefix has provisional approval for the desensitisation treatment of highly sensitised adult kidney transplant candidates prior to kidney transplantation from a donor against whom there is a positive cross-match. The use of Idefix should be reserved for patients who are otherwise unlikely to receive a kidney transplant.

The population is a subset of the most highly sensitised patients with end-stage kidney disease (ESKD) who have little to no access to life-saving kidney transplantation, because of a lack of immunologically suitable donors. Finding a match for these patients can be particularly difficult within a reasonable time or ever, meaning they spend a longer average time on transplant waiting lists, and therefore have an increased risk of dying on dialysis while waiting for a suitable donor.

MSAC in the PSD noted "The current population restriction [initial application] was not restricted to those with a clinical need. Patients with cPRA from 95% to less than 99%, who have the highest rate of transplantation given recent changes in allocation algorithms, should not be included in the eligible population. Eligibility should be restricted to patients with cPRA of 99% or more. MSAC noted that while PASC had previously endorsed a cPRA \geq 95% this had been before the impacts of the recent amendment to the allocation algorithm could be assessed. MSAC suggested that the applicant consider revising the population restriction to that as framed in the recommendation from the National Institute for Health and Care Excellence (NICE), UK to restrict use to "those who have a positive crossmatch with the donor and are unlikely to have a transplant under the available kidney allocation system (including prioritisation programmes for highly sensitised people)." MSAC suggested that such a definition, after accounting for the new algorithm, might limit the eligible population on the DD waiting list to those with cPRA of 99% or more and who have been on the waitlist for more than two years (that is, HS patients who have not received a kidney despite prioritisation) and limit the eligible population who are potential recipients of LD kidneys to those with cPRA of 99% or more who have failed plasma exchange desensitisation treatment so that it is a second line treatment for those who are potential recipients of LD kidneys. The applicant has taken heed of the MSAC advice and modified the eligible patient population accordingly and will apply alternate scenarios for MSAC consideration in the Applicant Development Assessment Report.

NB MSAC SECRETARIAT:

The applicant kindly requests confirmation of an exemption from returning to the PICO Advisory Sub Committee, (PASC) noting that the applicant was only advised to return to the Evaluation Sub Committee ESC prior to returning to MSAC. The revised Population will be the MSAC proposed population, the Intervention, imlifidase, is unchanged and the Outcome measures for the PICO

are unchanged. The Comparator is proposed to remain the Comparator agreed in the Ratified PICO Confirmation with the rationale addressed in the PICO set Comparator section.

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

Eligible patients are highly sensitised adult kidney transplant candidates and unlikely to be otherwise transplanted, either on the ANZKX or OrganMatch waitlist (despite the highly sensitised patients receiving prioritisation on organ allocation algorithms).

For patients on the **deceased donor** list, highly sensitised and unlikely to be transplanted can be defined as:

- Highly sensitised (cPRA \geq 99%) adult patients, AND
- With a positive crossmatch against an available donor, AND
- Have been on the deceased donor transplant list for at least 2 years.

For patients with a **living donor**, high sensitised unlikely to be transplanted can be defined as:

- Highly sensitised adult patients (cPRA \geq 99%), AND
- With a positive crossmatch against an available living donor AND
- Whom desensitisation regimens for organ transplantation are contraindicated or have failed, OR
- based on clinical judgement and experience, plasmapheresis /IVIG/ rituximab based desensitisation regimens are considered unlikely to provide a sufficient decrease in antibodies to enable transplantation. OR
- plasmapheresis / IVIG / rituximab-based desensitisation regimens are not logistically compatible with the patient's circumstance or the organization of the transplant centre.

General considerations before the use of imlifidase include:

- There is a benefit-risk profile favourable to desensitisation with imlifidase and subsequent transplantation versus remaining on the dialysis.
- The magnitude of incompatibility (immunological risk) between recipient and donor has been considered reasonable by the hospital's multidisciplinary team of experts.
- The patient understands and is willing to consider a higher immunological risk transplant, i.e., informed consent to the procedure and to post-transplant management.
- Imlifidase is to be given in a specialist centre with experience of treating highly sensitised patients.

Provide a rationale for the specifics of the eligible population:

The reader is directed to the initial Application Form and the Ratified PICO Confirmation and the MSAC PSD for a more detailed discussion on the rationale for the eligible population. All available on the MSAC website under application 1732

Kidney transplantation is the optimal treatment for patients with kidney failure since it increases patient survival and quality of life and is cost effective compared to continuing dialysis (Montgomery RA et al., 2005, Montgomery RA et al., 2011, Vo AA et al., 2013, Orandi BJ et al., 2016). Many of the advantages of transplantation over dialysis are linked to the availability of a functioning kidney, such as halting cardiovascular disease progression in patients with ESRD (Meier-Kriesche HU et al., 2004). Continued dialysis presents with long-term complications i.e., amyloidosis, bone disease, endocrine disturbances, infection, cardiovascular complications, vascular access, and nutrition complications (Sinnakirouchenan R and Holley JL, 2011, Cozzolino M et al., 2018). As the average age and comorbidity profile of dialysis patients continues to increase, a greater proportion of those on dialysis are deemed medically unsuitable for transplantation (Cass et al., 2006).

Highly sensitised patients with end-stage kidney disease (ESKD) have little to no access to life-saving kidney transplantation, because of a lack of immunologically suitable donors. Finding a match for these patients can be particularly difficult within a reasonable time or ever, meaning they spend a longer average time on transplant waiting lists, and therefore have an increased risk of dying on dialysis while waiting for a suitable donor.

The Australian kidney allocations systems attempts to address this inequity by prioritising the highly sensitised patient. All kidneys retrieved from deceased donors are initially allocated based on a national formula that prioritises sensitised patients (Figure 1), well-matched kidney and paediatric patients and addresses interregional sharing imbalances (Sypek et al., 2021)

Since the allocation algorithm update in May 2021 and referencing data presented at the MSAC meeting, it is now apparent that clinical need has changed from the original public funding application for patients with cPRA ranging from 95% to less than 99%. Based on data from the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA) this group now has the highest rate of transplantation (71% in May 2021) of any group, and there are few of these patients on the transplantation waitlist (n = 58, or 4% of the total waitlist in 2021). However, the need for imlifidase in the cPRA \geq 99% remains. In 2021, approximately 11% (n = 153) of the 1,338 people on the Australian kidney transplant waitlist had cPRA of 99% or more, and 140 of those had been on the waitlist for two or more years. MSAC noted in the PSD there was an unmet clinical need for highly sensitised patients to be able to receive donor kidneys and move off dialysis, and that imlifidase treatment is the only option that can increase equity of access for highly sensitised patients with cPRA \geq 99% who may otherwise remain on dialysis for a long time waiting for a suitable donor, despite being prioritised.

Figure 1 Australian National Kidney Transplant Allocation Formula

Kidney allocation algorithms

National Allocation formula

Match level	Description	Criteria	Base score
1	Very Highly sensitised ABO Compatible	1a mPRA ≥ 99.7	99 700 000
		1b mPRA ≥ 99	99 000 000
		1c mPRA ≥ 98	98 000 000
		1d mPRA ≥ 97	97 000 000
		1e mPRA ≥ 96	96 000 000
		1f mPRA ≥ 95	95 000 000
National Urgent	ABO Compatible	Recipient National urgency >0	90 000 000
2	EPTS restriction HLA matching Prioritises Low EPTS recipients Matched at HLA DRB1 ABO Matched KDPI max value is applied from this level down	2a 0 mismatches HLA-A or HLA-B and EPTS ≤ 25	89 000 000
		2b 1 mismatch HLA-A or HLA-B and EPTS ≤ 25	88 000 000
		2c 2 mismatch HLA -A or HLA-B and EPTS ≤ 25	87 000 000
		2d 0 mismatches HLA -A or HLA-B and EPTS ≤ 60	86 000 000
3	HLA matching Highly Sensitised	3a 0 mismatch at HLA A or HLA B or HLA DRB1 and mPRA >80	79 000 000
		3b 1 mismatch at HLA A or HLA B or HLA DRB1 and mPRA >80	78 000 000
		3c 2 mismatches at HLA A or HLA B or HLA DRB1 and mPRA >80	77 000 000
	HLA Matching Centre credit difference	3d Matched at HLA DRB1 1 mismatch HLA A or HLA B And mPRA ≤ 80 And Centre credit difference ≤ -3	76 000 000
		3e Matched at HLA DRB1 2 mismatch HLA A or HLA B And mPRA ≤ 80 Centre credit difference ≤ -6	75 000 000
		3f mPRA >80 Centre credit difference ≤ -9	74 000 000
		3g Centre credit difference < -20	73 000 000

Intervention

Name of the proposed health technology:

Imlifidase (Idefirix®)

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

Once a patient is considered eligible for imlifidase, the key components and clinical steps are:

- 1) Consent must be provided prior to undergoing desensitisation. It is proposed, as is standard practice, that pre-consent is given before imlifidase is administered.
- 2) Obtain transplant organ:
 - i) If a Deceased Donor transplant, proactively delist unacceptable antigen/s on OrganMatch and accept allocated Deceased Donor organ, admit transplant recipient.
 - ii) Surgical donor organ suitability assessed when organ arrives at transplant centre.
 - iii) If Living Donor, admit recipient and donor.
- 3) Premedication administered: corticosteroids, and antihistamines to transplant recipient.
- 4) Imlifidase is administered via an infusion. This occurs over 15 minutes and as early as practicable once a viable organ is confirmed.
- 5) Collect and send sera at 2 and 4 hours post imlifidase infusion to the HLA laboratory. [Process 2-hour sera (the result will be available at 4-5 hours post-infusion). If the 2-hour sera is negative (<1000 MFI), proceed with transplant. There is no need to perform Luminex test for the 4-hour sample. If the 2-hour sera shows a singular DSA of >4,000 MFI (local exclusion threshold for kidney transplant in Australia), order the Luminex test for the 4-hour sera. If the DSA is still positive (>4000 MFI), consider a second dose of imlifidase. If the DSA from the 4-hour sera is 1000-4000 MFI (i.e. 6-7 hours post infusion) the patient can still be transplanted. (Expert Australian Opinion)]
- 6) If living donor proceed with Living Donor kidney explantation.
- 7) Proceed with organ recipient transplant surgery.

Identify how the proposed technology achieves the intended patient outcomes:

The intended patient outcome is a kidney transplant in a patient who would otherwise remain on dialysis. Imlifidase is a novel desensitisation therapy derived from *Streptococcus pyogenes* that cleaves immunoglobulin G (IgG) molecules, enabling kidney transplantation in highly sensitised patients. Imlifidase provides a rapid, effective, and convenient means for desensitisation within a few hours, converting patients from crossmatch positive to an available donor, to negative, enabling transplantation in a patient population who would otherwise remain on dialysis for life or die waiting for a kidney transplant. Imlifidase works consistently across different levels of sensitisation and baseline DSAs; even for the most highly sensitised patients (cPRA ≥99%).

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components? (please select your response)

- Yes
 No

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

Imlifidase is a patent protected agent and there are no other IgG cleaving enzymes available.

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): (please select your response)

- Yes
 No

Provide details and explain:

Per the TGA approved Product Information imlifidase should be prescribed and supervised by specialist physicians experienced in the management of immunosuppressive therapy and of sensitised renal transplant patients. Imlifidase is restricted to hospital use only. After treatment with imlifidase, crossmatch conversion from positive to negative should be confirmed before transplantation. Each clinic should follow its standard protocol for confirmation of crossmatch conversion from positive to negative. Proximity to HLA laboratories for timely results post imlifidase administration is a consideration weighed against prolong cold ischemia time. One dose is adequate for crossmatch conversion in the majority of patients but, if needed, a second dose can be administered within 24 hours after the first dose. In the phase 2 clinical trials, a small proportion of patients (6.5%: 3/46 patients) received administration of an additional dose within 24 hours of the first dose. Expert Opinion suggests that if, at 4 hours post imlifidase infusion, singular DSA >1,000 MFI (but <4,000 MFI), perform intra-operative DSA. If the DSA is still positive, i.e., >4000 MFI, consider a second dose of imlifidase. If the second sample (4 hour) DSA is 1000 – 4000 MFI, the patient can still be transplanted.

Premedication with corticosteroids and antihistamines should be given to reduce the risk of infusion reactions in accordance with transplant centre routines.

The temporary reduction of IgG by imlifidase must be taken into consideration. The most common infections in patients with hypogammaglobulinemia are respiratory tract infections. Therefore, in addition to the standard of care infection prophylaxis in kidney transplantation in general (against *Pneumocystis carinii*, cytomegalovirus and oral candida), all patients should also receive prophylactic oral antibiotics covering respiratory tract pathogens for 4 weeks. Should a patient for any reason not be transplanted after imlifidase treatment, prophylactic oral antibiotics covering respiratory tract pathogens should still be given for 4 weeks.

Patients treated with imlifidase should, in addition, receive standard of care induction T-cell depleting agents with or without B-cell depleting agents (see Product Information Section 5.1 Pharmacodynamic properties), i.e. imlifidase does not eliminate the need for standard of care immunosuppressive therapy.

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

A transplant nurse will administer the iv infusion of imlifidase under the supervision of a transplant nephrologist or transplant surgeon.

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

Not applicable

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

Treatment should be prescribed and supervised by specialist physicians experienced in the management of immunosuppressive therapy and of sensitised renal transplant patients.

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? (please select your response)

- Yes
 No

Provide details and explain:

Treatment should be prescribed and supervised by specialist physicians experienced in the management of immunosuppressive therapy and of sensitised renal transplant patients per the TGA approved Product Information.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:
(select all relevant settings)

- 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? (please select your response)

- Yes
 No

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

Provide a response if you answered 'No' to the question above

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 health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:
(please copy the below questions and complete for each comparator)

Please provide a name for your comparator:

Current care in the absence of imlifidase: dialysis until a transplant becomes available.

Please provide an identifying number for your comparator (if applicable):

Specify the identifying number here

Please provide a rationale for why this is a comparator:

Highly sensitised and unlikely to be transplanted patients will remain on the transplant waitlist and continue to receive dialysis (haemodialysis or peritoneal), until a transplant becomes available (as these patients are on the active waiting list), which may or may not occur. Transplants may rarely occur but at a very decreased rate compared to the intervention).

MSAC in the PSD on page 10 considered "that insufficient attention was placed on potential alternatives as comparators including plasma exchange and other desensitisation protocols for patients who are LD and DD kidney recipients and desensitisation enabling participation in paired exchange with Living Related Donors (LRDs)."

The applicant and PICO Advisory Sub-Committee as outlined in the Ratified PICO Confirmation agreed that off-label desensitisation regimens were not an appropriate comparator for imlifidase.

The Applicant would like to reinforce that no desensitization regimens or agents are registered by the TGA for such use and are therefore considered experimental.

Off label desensitisation regimens are especially inappropriate in the deceased donor setting, as they require several sessions of PLEX / IVIG with multiple hospital visits and associated DSA

testing over several weeks or even months depending on the level of HLA sensitisation and the availability of the patient. Acceptance and transplant of an offered organ is temporally unpredictable and under time constraints driven by the detrimental impact of prolonged cold ischemia time.

Unlicensed, off label desensitisation regimens are inconsistent across institutions with limited efficacy in reducing DSA as outlined in the Ratified PICO confirmation. PASC discussed whether the current desensitisation regimen was an appropriate comparator for a sub-population of those patients on the living donor list who currently would be offered off-label desensitisation regimens. It was noted by the applicant's expert, who is the HLA lab director for NSW, VIC and SA, and highly familiar with current clinical practices advised that it is not often, and decreasingly offered as only about 40% of attempts were successful and clinicians would not consider this a suitable therapy option for all patients, with only a small sub-population expected to respond.

To reflect this, the applicant has proposed the following eligibility criteria for potential adult living donor eligible patients:

- Have a calculated Panel Reactive Antibody test (cPRA) $\geq 99\%$, AND
 - With a positive crossmatch against an available living donor AND
 - Whom desensitisation regimens for organ transplantation have failed or are contraindicated
- OR
- based on clinical judgement and experience, plasmapheresis / IVIG / rituximab-based desensitisation regimens are considered unlikely to provide a sufficient decrease in antibodies to enable transplantation
- OR
- plasmapheresis / IVIG / rituximab-based desensitisation regimens are not logistically compatible with the patient's circumstance or the organisation of the transplant centre.

At the MSAC meeting in July 2023, as outlined in the PSD page 6 "MSAC noted that PASC had also previously considered but not recommended inclusion of other desensitisation regimes as comparators for LD patients because components of these regimes are used off label and use is variable across the country (i.e., there is no one standard regime that could be considered as standard of care). However, MSAC considered that there were several desensitisation protocols in clinical use for HS patients who are potential recipients of LD and DD kidneys in addition to participation in the paired kidney exchange (for LD kidneys), and many agents were in current clinical use for this indication. MSAC considered that desensitisation protocols (IVIG, rituximab, plasma exchange) were a comparator for Imlifidase, noting the likely cost differential between these agents and imlifidase'. The Applicant investigated the veracity of the statement "that there were several desensitisation protocols in clinical use for HS patients who are potential recipients of LD and DD kidneys... and ... are in current clinical use" via a survey to all 15 adult renal transplant centres. The survey had 11 of the 15 adult kidney transplant centres responding, which represents 92% of the transplant universe in Australia. Forty-five percent (45%) of the centres said they had not attempted desensitisation regimens in the past 12 months for a patient with a mean fluorescent intensity (MFI) of >4000 . Of those centres that did attempt desensitisation regimens, it was only offered on average to less than 20% of highly sensitised patients. Eighty-two percent

(82%) of respondents cited an anticipated inadequate response for not offering currently available desensitisation regimens. One verbatim response is emblematic of the Australian situation, "We attempted desensitisation protocols for a few of our highly sensitised patients during 2019-2021, there was inadequate response to desensitisation and did not result in transplantation." Considering these observations, the Applicant proposes to retain the PASC endorsed comparator which is the current care in the absence of imlifidase. These patients (on the active waiting list) will remain on the transplant waitlist and continue to receive dialysis (haemodialysis or peritoneal) until a transplant becomes available, which may or may not occur (transplants will occur but at a decreased rate compared to the intervention). It is the applicants conjecture that desensitisation regimens are not common clinical practice for the population that would be considered eligible for imlifidase.

The applicant therefore considers that the appropriate comparator is current care in the absence of imlifidase: i.e., dialysis until a transplant becomes available.

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? (please select your response)

- 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 in all cases
- Full – subjects who receive the proposed intervention will not receive the comparator

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

With the availability of imlifidase, some patients will be able to be removed from dialysis and become kidney transplant recipients. However, donor organ availability is constrained so most highly sensitised patients would remain on dialysis. Over time it is expected that the current population of imlifidase eligible Highly Sensitised patients would diminish and reach more or less steady state based on the incidence of new highly sensitised patients entering the waitlists. This may take many years.

Highly Sensitised patients maintain a register of unacceptable antigens in organMatch which in the usual course of transplantation they cannot accept in the donor kidney. In consultation with the HLA labs experts the transplant nephrologist needs to select and then proactively delist from the register one or more of the unacceptable antigens. These are the antigens the nephrologist will be willing to accept in the donor kidney under the protection of imlifidase. Thus, there is a significant amount of clinician control in an imlifidase enabled transplant and comparator substitution.

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

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

The applicant refers to the Ratified PICO Confirmation for Outcomes of relevance. Achieving durable transplant in sensitised patients and especially outcomes on graft survival and graft function, are considered the most clinically relevant outcome parameters (EMA 2020), along with the all-important patient survival. The outcomes identified in the ratified PICO were:

Safety	Anaphylactic or acute infusion reactions from imlifidase infusion (number of times infusion needs to be ceased for treatment Serious infection, particularly respiratory infection · Failure to desensitise · Antibody mediated rejection (AMR) and treatment required
Effectiveness suggested by the ADA	Efficacy of crossmatch conversion from positive to negative crossmatch (this should be a pre-transplant outcome) Graft survival Kidney function (eGFR) Adverse effects of treatment Health-related quality of life
Immediate post-transplant	Proportion of patients with cPRA \geq 95% who received a transplant. Graft viability Acute antibody mediated rejection (AMR) Duration of time on waiting list for patients who receive a transplant
The following outcomes to be reported in the immediate-, medium- and longer-term	Graft survival Patient survival Proportion of patients on dialysis and/or reduced time on dialysis · Hospitalisation AMR (outcome reported to OrganMatch site)

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)? (please select your response)

- Superior
 Non-inferior

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

Imlifidase helps enable equity of access to kidney transplantation for a small number of highly sensitised patients who are unable to be transplanted despite being prioritised in available kidney allocation systems.

Imlifidase allows a rapid, profound, and reversible reduction of DSAs with acceptable safety risks thereby converting a positive cross match into negative, enabling transplants in patients highly sensitised against a broad range of HLAs and unlikely to be otherwise transplanted. After complete administration of imlifidase all patients that were crossmatch-positive before treatment with imlifidase were converted to negative within 24 hours (Imlifidase TGA approved Product Information – Clinical Trial Section). The rapid efficacy of imlifidase is important as it allows a transplant to proceed within the small window instead of dialysis or other off-label desensitisation regimens such as plasmapheresis or IVIg, that requires several hospital visits and testing over several weeks or months that have limited efficacy in reducing DSA.

With the availability of imlifidase, some patients will be able to be removed from lifelong debilitating dialysis. The survival advantage of kidney transplantation compared with dialysis is estimated to be 13.8 years (95% CI: 11.4-16.2) (Zhang Y et al., 2020). Health improvements include reduced risk of death, and decreased morbidity, especially cardiac events associated with dialysis. Patients also report a better quality of life after transplant.

Imlifidase was well tolerated, converted positive crossmatches to negative, and enabled patients that are highly sensitised and unlikely to be transplanted to undergo kidney transplantation, with good kidney function and patient and graft survival.

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

With the availability of imlifidase, patients will be able to be removed from debilitating dialysis and become kidney transplant recipients. Dialysis has a significant impact on a patient's morbidity, mortality and quality of life.

Identify how the proposed technology achieves the intended patient outcomes:

Imlifidase helps enable equity of access to kidney transplantation for a small number of highly sensitised patients who are unable to be transplanted despite being prioritised in available kidney allocation systems.

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

(please select your response for each statement)

- | | | |
|---|---|-----------------------------|
| A change in clinical management? | <input checked="" type="checkbox"/> Yes | <input type="checkbox"/> No |
| A change in health outcome? | <input checked="" type="checkbox"/> Yes | <input type="checkbox"/> No |
| Other benefits? | <input checked="" type="checkbox"/> Yes | <input type="checkbox"/> No |

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

In relation to equity of access imlifidase enables to a small subset of highly sensitised patients, as per the ratified PICO confirmation and MSAC PSD: The commentary concurred with the ADAR that equity considerations are pertinent to using imlifidase in HS patients. Notably, pregnancy is a significant factor contributing to sensitisation, putting women, particularly mothers, at a higher risk of being highly sensitised and potentially facing disadvantages in accessing kidney transplantation. The commentary agreed that employing imlifidase would help promote equity between genders and among women with and without history of pregnancy. The commentary observed that certain patient groups, such as Aboriginal and Torres Strait Islander patients and other ethnic minorities, are more likely to be highly sensitised and remain on waiting lists for extended periods, with minimal prospects for transplantation. This also raises equity concerns. The commentary concurred with the ADAR that employing imlifidase helps to achieve a more equitable allocation of kidneys for Aboriginal and Torres Strait Islander patients and those within other minority ethnic groups.

In the absence of imlifidase these majority of these eligible patients remain on long term dialysis which has a significant impact on a patient's morbidity, mortality, and quality of life

Transplant recipients are able to return to satisfying, productive income generating and tax paying work when they are freed from the obligation of conducting hours long dialysis procedures multiple time per week.

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? (please select your response)

- More costly
- Same cost
- Less costly

Provide a brief rationale for the claim:

In the absence of imlifidase the vast majority of eligible patients (as per the criteria outlined above) incur the cost of renal replacement therapy and the complications associated with its long-term use (impacting patient morbidity, mortality and quality of life).

Imlifidase can be demonstrated to be a cost-effective treatment option demonstrated by cost utility modelling. The following cost would be incurred for the small subset of highly sensitised patients who are now enabled access to transplantation instead of remaining on long term dialysis:

The cost of imlifidase: The applicant requested price per vial of imlifidase (11mg power for concentrate for solution for infusion) is A\$**redacted**. However, the applicant will rigorously

explore all the commercial terms recommended in the PSD by MSAC, within the Applicant Developed Assessment Report to be submitted in February 2024. E.g., Per patient pricing

Imlifidase would also require specific low-cost co-medication (Antihistamines, Corticosteroids, Prophylactic antibiotics), and an additional Luminex single antigen bead testing or flow cytometry cross match.

In line with standard Australian clinical practice for all kidney transplantations, post transplants will require immunosuppressive regimens and post-transplant care/intensive follow up based on the Renal Association Clinical Practice guideline in post-operative care in the kidney transplant recipient (Baker, Mark et al. 2017).

Summary of Evidence

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

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1	Phase 2, single-centre, open-label, uncontrolled, non-randomised, ascending-dose study	13-HMedIdeS-02 Phase 2 Study, Evaluation of Safety and Efficacy of IdeS in Chronic Kidney Disease ClinicalTrials.gov identifier: NCT02224820 Lorant T, Bengtsson M, Eich T, Eriksson BM, Winstedt L, Järnum S, Stenberg Y, Robertson AK, Mosén K, Björck L, Bäckman L, Larsson E, Wood K, Tufveson G, Kjellman C. Safety, immunogenicity, pharmacokinetics, and efficacy of degradation of	N=8 Evaluation of safety and efficacy of imlifidase in patients with CKD and on transplant waiting list. Ascending doses (0.12 mg/kg or 0.25 mg/kg, ± second dose) were used. All	Lorant et. al.	2018

		<p>anti-HLA antibodies by IdeS (imlifidase) in chronic kidney disease patients. Am J Transplant. 2018 Nov;18(11):2752-2762. doi: 10.1111/ajt.14733. Epub 2018 Apr 17. PMID: 29561066; PMCID: PMC6221156.</p>	<p>patients showed IgG degradation, with anti-HLA antibodies substantially reduced. The safety and tolerability were demonstrated in the study. Prior desensitisation.</p>		
2	<p>Phase 2, single-centre, open-label, uncontrolled, non-randomised, ascending-dose study</p>	<p>13-HMedIdeS-03 Study to Evaluate the Safety, Tolerability, Efficacy and PK of IdeS in kidney Transplantation ClinicalTrials.gov identifier: NCT02475551 Jordan SC, Lorant T, Choi J, Kjellman C, Winstedt L, Bengtsson M, Zhang X, Eich T, Toyoda M, Eriksson BM, Ge S, Peng A, Järnum S, Wood KJ, Lundgren T, Wennberg L, Bäckman L, Larsson E, Villicana R, Kahwaji J, Louie S, Kang A, Haas M, Nast C, Vo A, Tufveson G. IgG Endopeptidase in Highly Sensitised Patients Undergoing Transplantation. N Engl J Med. 2017 Aug 3;377(5):442-453. doi: 10.1056/NEJMoa1612567. Erratum in: N Engl J Med. 2017 Oct 26;377(17):1700. PMID: 28767349.</p>	<p>N= 10 Evaluation of safety, tolerability, efficacy, and PK of single dose imlifidase (0.25 mg/kg or 0.50mg/kg) in highly sensitised patients with CKD in Sweden. Efficacy was defined as HLA antibody levels acceptable for transplanting. All 10 patients were transplanted. Both doses well tolerated.</p>	<p>Jordan et. al. Amalgamated journal article from studies:</p> <ul style="list-style-type: none"> • 13-HMedIdeS-02, • 13-HMedIdeS-03, 14-HMedIdeS-04 	2017

			The 0.25mg/kg dose was assessed as the most favourable benefit-risk ratio. No prior desensitisation.		
3	Phase 2, uncontrolled, single-centre, single-arm, open-label, investigator-initiated study	<p>14-HMedIdeS-04</p> <p>IdeS in Highly Sensitised Patients Awaiting Kidney Transplantation ClinicalTrials.gov identifier: NCT02426684</p> <p>Jordan SC, Lorant T, Choi J, Kjellman C, Winstedt L, Bengtsson M, Zhang X, Eich T, Toyoda M, Eriksson BM, Ge S, Peng A, Järnum S, Wood KJ, Lundgren T, Wennberg L, Bäckman L, Larsson E, Villicana R, Kahwaji J, Louie S, Kang A, Haas M, Nast C, Vo A, Tufveson G. IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation. <i>N Engl J Med.</i> 2017 Aug 3;377(5):442-453. doi: 10.1056/NEJMoa1612567. Erratum in: <i>N Engl J Med.</i> 2017 Oct 26;377(17):1700. PMID: 28767349.</p>	<p>N=17</p> <p>Evaluation of safety and tolerability of imlifidase to eliminate DSAs and prevent antibody-mediated rejection post-transplant in highly sensitised patients. The reduction or elimination of DSAs allowed transplantation in all patients. A single graft loss occurred due to hyperacute rejection caused by a non-HLA, non-IgG antibody. Most patients had undergone one or more prior</p>	Jordan et. al.	2017

			sessions of desensitisation.		
	Phase 2, multi-centre, open label, uncontrolled study Mixed prior desensitisation	<p>15-HMedIdeS-06 A Phase 2 Study to Evaluate the Efficacy of IdeS to Desensitise Transplant Patients with a Positive Crossmatch test (Highdes). ClinicalTrials.gov Identifier: NCT02790437 EudraCT Number: 2016-002064-13</p> <p>Lonze BE, Tatapudi VS, Weldon EP, Min ES, Ali NM, Deterville CL, Gelb BE, Benstein JA, Dagher NN, Wu M, Montgomery RA. IdeS (Imlifidase): A Novel Agent That Cleaves Human IgG and Permits Successful Kidney Transplantation Across High-strength Donor-specific Antibody. <i>Ann Surg.</i> 2018 Sep;268(3):488-496. doi: 10.1097/SLA.00000000000002924.</p> <p>Jordan SC, Legendre C, Desai NM, Lorant T, Bengtsson M, Lonze BE, Vo AA, Runström A, Laxmyr L, Sjöholm K, Schiött Å, Sonesson E, Wood K, Winstedt L, Kjellman C, Montgomery RA. Imlifidase Desensitization in Crossmatch-positive, Highly Sensitised Kidney Transplant Recipients: Results of an International Phase 2 Trial (Highdes). <i>Transplantation.</i> 2021</p> <p>Follow-up to 3-years: Kjellman C, Maldonado AQ, Sjöholm K, Lonze BE, Montgomery RA, Runström</p>	<p>N=19 Evaluation of efficacy and safety of imlifidase in patients who are on the waiting list for kidney transplant and have previously failed or likely to fail desensitisation. 5 Living Donor and 13 Deceased Donor transplants were performed within the study. Patient survival was 100% with graft survival of 88.9% at 6 months One patient did not receive full dose treatment due to allergic reaction.</p>	<p>Lonze et. al.</p> <p>Jordan et. al.</p> <p>Kjellman et al</p>	<p>2018</p> <p>2021</p> <p>2021</p>

		A, Lorant T, Desai NM, Legendre C, Lundgren T, von Zur Mühlen B, Vo AA, Olsson H, Jordan SC. Outcomes at 3 years posttransplant in imlifidase-desensitized kidney transplant patients. Am J Transplant. 2021 Dec;21(12):3907-3918. doi: 10.1111/ajt.16754. Epub 2021 Jul 19. PMID: 34236770.			
Yet-to-be-published research that may have results available in the near future					
	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***

1.	Prospective Observational, Long Term Follow up Study	<p>20-HMedIdeS-14 A Follow up Study of Patients Treated with Imlifidase Prior to Kidney Transplantation</p> <p>Clinicaltrials.gov identifier: NCT03611621</p> <p>An ongoing, prospective, observational, long-term follow up study to evaluate graft survival and clinical outcomes among patients treated with IV imlifidase prior to kidney transplantation in the four imlifidase studies. Data collected at Year 1,2 & 5 after the first dose of imlifidase.</p> <p>Follow up to 5 years - not yet published but Clinical Trial Report utilised for this appraisal</p> <p>Follow-up to 3-years (This is not an official publication of the study 14, but it includes a subset of study 14 data): Kjellman C, Maldonado AQ,</p>	<p>N=39 The aim is to collect data from extended follow up in subjects that have received a kidney transplant following imlifidase dosing to provide a better understanding regarding the long-term outcome for these subjects. Collected were data on parameters such as patient and graft survival, comorbidity, treatment of graft rejection episodes and quality of life as well as anti-drug antibody levels.</p>	<p><u>NCT03611621</u> Kjellman et al</p>	Dec 2022
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		<p>Sjöholm K, Lonze BE, Montgomery RA, Runström A, Lorant T, Desai NM, Legendre C, Lundgren T, von Zur Mühlen B, Vo AA, Olsson H, Jordan SC.</p> <p>Outcomes at 3 years posttransplant in imlifidase-desensitised kidney transplant patients. Am J Transplant. 2021 Dec;21(12):3907-3918. doi: 10.1111/ajt.16754. Epub 2021 Jul 19. PMID: 34236770.</p>			
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2.	Phase 3, open-label, controlled, randomised	20-HMedIdeS-17 Renal Function in Highly Sensitised Patients 1 Year After Desensitization with Imlifidase Prior to DD Kidney Tx (ConfldeS) Clinicaltrials.gov identifier: NCT04935177	N=64 A USA exclusive study evaluating 12-month kidney function in highly sensitised (cPRA \geq 99.9%) kidney transplant patients with positive crossmatch against a deceased donor, comparing desensitisation using imlifidase with standard of care (i.e., the desensitisation protocol currently in use at the respective study site). Recruitment started. Also known as the ConfldeS trial.	<u>NCT04935177</u>	Oct 2024
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3.	Open-label, post-authorisation efficacy and safety study	20-HMedIdesS-19 A Controlled, Open-label PA Efficacy and Safety Study in Imlifidase Desensitised Kidney Tx Patients With Positive XM Against a Deceased Donor Prior to Imlifidase Treatment, Including Non-comparative Registry and Concurrent Reference Cohorts ClinicalTrials.gov Identifier: NCT05369975 EudraCT Number: 2021-002640-70	N=50 imlifidase N=175 normal transplantation routine A post approval efficacy study to evaluate the 1-year graft survival, 1 year kidney function, and safety in kidney transplanted patients with DSA, who have been treated with imlifidase. (EU conditional approval requirement).	<u>NCT05369975</u>	Dec 2024
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* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

**Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes. For yet to be published research, provide high level information including population numbers and whether patients are being recruited or in post-recruitment.

*** If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).

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 reader is referred to the Ratified PICO Confirmation. The current clinical management pathway for highly sensitised ESKD patients waiting for a transplant is dialysis. The two main modalities for dialysis are haemodialysis (HD) and peritoneal dialysis (PD), with the majority of patients on HD in a facility (75%), followed by PD (17%) and HD at home (8%) (ANZDATA Registry, 2020a, ANZDATA Registry, 2020b). The majority (90%) of haemodialysis is delivered as high-flux conventional, thrice weekly, in a dialysis facility. Treatment times are typically (for 92% of patients) between 4 and 5 hours, with majority of patients requiring dialysis more than 3 times per week (Damasiewicz and Polkinghorne, 2020).

Transplant listing

In Australia, ESKD patients are referred to transplant centres by their local treating nephrologist. These transplant centres conduct the candidate assessment, assessment of any potential living donors, waitlist management, transplant surgery, and acute post-transplant care (Wyld MLR et al., 2021). The transplant assessment process in Australia mirrors that performed internationally and is largely consistent with KDIGO Guidelines (Chadban et al., 2020), with a focus on a patient's physical and psychological suitability for transplantation. Some patients are not deemed suitable for transplantation; this is not the patient population of interest.

Maintenance on the waitlist

Patients that have no living donor available (or for whom the ANZKX is not an alternative), enter the deceased donor matching (OrganMatch) programme to wait for a sufficiently compatible deceased donor organ. While on the waiting list, patients are managed with dialysis. The treating nephrologist or dedicated consultant physician will plan and manage the patient's dialysis through regular ordering, performing and interpreting appropriate biochemical and haematological studies, generally monthly. Results are provided to the patient's treating General Physician. Relevant adjustments to medications and dialysis therapies will be made based upon these results. The overseeing transplant nephrologist will also co-ordinate regular investigations required to keep patient on active transplantation lists, and where relevant refer to other specialists involved in the care of the patient.

Patients may also evaluate a living donor option, or they could also enter the ANZKX if they have a living donor who is willing to donate one of their kidneys but is unable to do so due to insurmountable HLA incompatibility. The ANZKX will match incompatible kidney donor and recipient pairs with other incompatible pairs across Australia and New Zealand. These patients are also often entered onto the deceased donor list. While searching for a compatible living donor, or matched kidney exchange donor, patients are managed with dialysis.

Patients that are positively virtually crossmatched against an available donor, may undergo an experimental desensitisation regimen. If DSA levels remain unacceptable despite desensitisation

attempts, they will remain on dialysis. Over time some patients will become too sick to remain on the waiting list and will be delisted from the waitlist.

The current and proposed management algorithms included in this resubmission Application From are those outlined in Appendix A (p35 and p36) of the Ratified PICO Confirmation with an amended population to restrict the Population to those with a cPRA greater or equal to 99%.

The applicant is working with the Renal Transplant Advisory Committee under the auspices of the Transplantation Society of Australia and New Zealand, on an Australian specific 'protocol' to be developed around patient eligibility criteria, logistical considerations, and post-transplant management.

Figure 2: Current management algorithm

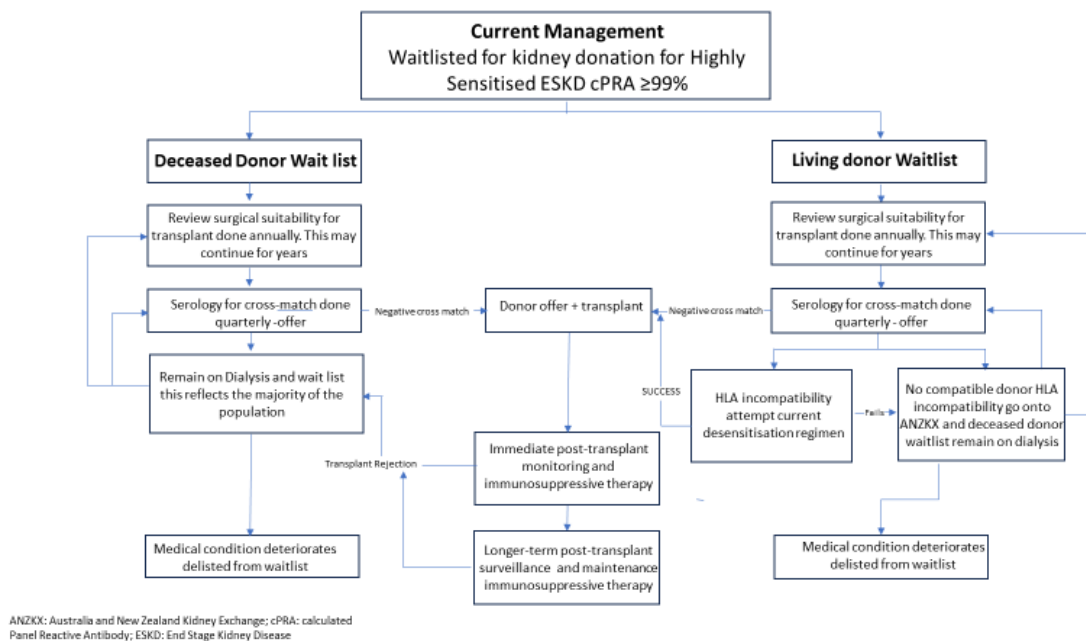
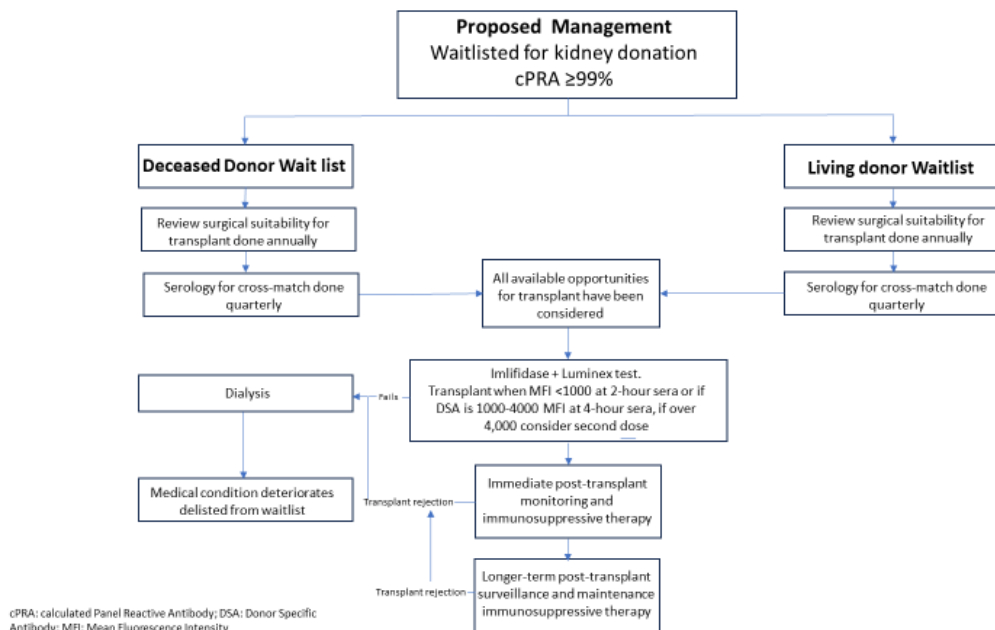


Figure 3: Proposed management algorithm



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?

(please select your response)

- Yes
 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:

The majority of eligible patients will receive ongoing renal replacement therapy as opposed to the opportunity of a kidney transplantation.

Comparing the current kidney transplantation algorithm to the proposed management algorithm; there will be an additional assessment of patients who have been on the donor transplant list for at least 2 years that meet the eligibility criteria outlined in the "Population" section of the Application Form. A successfully identified imlifidase candidate will undergo imlifidase iv administration and then follow routine transplant surgery. There will be more intensive immediate post-transplant procedure monitoring before reverting to routine transplant recipient monitoring.

Use of the health technology

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

- Imlifidase specific co-medication (Induction Therapy, Antihistamines, Corticosteroids, Prophylactic antibiotics)
- Imlifidase specific co-test: Luminex single antigen bead testing or flow cytometry cross match
- Treatment should be prescribed and supervised by specialist physicians experienced in the management of immunosuppressive therapy and of sensitised renal transplant patients.

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

The majority of patients receiving current care in the absence of imlifidase, will be incurring the ongoing and long-term costs/resources of renal replacement therapy.

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

The applicant is working with the Renal Transplant Advisory Committee under the auspices of the Transplantation Society of Australia and New Zealand, on an Australian specific 'protocol' to be developed around patient eligibility criteria, logistical considerations, and post-transplant management. The main difference in health care resource utilisation in proposed health care technology is the cost of imlifidase, the associated cross match conversion test (Luminex) and incremental immediate post-transplant monitoring and potentially management on antibody

mediated rejection which occurs in about a third of patients consequent to the return of Donor Specific Antibodies. AMRs were treated and resolved with standard therapies, most commonly plasmapheresis with or without the addition of intravenous immune globulin (IVIg), and optimization of maintenance immunosuppression. After the immediate post-transplant monitoring and management an imlifidase enabled transplant would utilise healthcare resources in a similar manner to any other compatible organ transplant, apart from more intensive monitoring, utilising Luminex SAB testing for DSA rebound (9 assessments) This would entail post-transplant immunosuppression of usually tacrolimus, a mycophenolate containing agent and low dose corticosteroids. There are periodic clinic visits to the transplanting centre once or more per year.

A dialysis patient would undergo institutional haemodialysis (75%) and peritoneal dialysis (17%), home dialysis (8%) (ANZDATA Registry, 2020a, ANZDATA Registry, 2020b). The majority (90%) of haemodialysis is delivered as high-flux conventional, thrice weekly, in a dialysis facility. Treatment times are typically between 4 and 5 hours, with majority of patients requiring dialysis more than 3 times per week. There is significant patient inconvenience and incrementally increasing morbidity and mortality associated with dialysis.

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:

In line with standard Australian clinical practice for transplantation, patients receiving the proposed technology will require:

- Post-transplant immunosuppressive regimens (as per the ratified PICO): Tacrolimus (the first year), Tacrolimus (subsequent years), Corticosteroids (all years), Mycophenolate mofetil (all years)
- Post-transplant care/intensive follow up based on the Renal Association Clinical Practice guideline in post-operative care in the kidney transplant recipient (Baker, Mark et al. 2017).
- For a small percentage of patients an additional Luminex test at four hours is required.

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

- The majority of patients receiving current care in the absence of imlifidase, will be incurring the ongoing and long-term costs/resources of renal replacement therapy.
- For the small proportion of imlifidase eligible highly sensitised patients who receive a kidney transplantation in the absence of imlifidase, they will also require:
 - Post-transplant immunosuppressive regimens (as per the ratified PICO): Tacrolimus (the first year), Tacrolimus (subsequent years), Corticosteroids (all years), Mycophenolate mofetil (all years)
 - Post-transplant care/intensive follow up based on the Renal Association Clinical Practice guideline in post-operative care in the kidney transplant recipient (Baker, Mark et al. 2017).

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

- The majority of patients receiving current care in the absence of imlifidase, will be incurring the ongoing and long-term costs/resources of renal replacement therapy.
- For the small proportion of imlifidase eligible highly sensitised patients who receive a kidney transplantation in the absence of imlifidase, they will require analogous monitoring, surveillance, and immunosuppressive treatment as per the proposed health technology.
- The applicant is working with the Renal Transplant Advisory Committee under the auspices of the Transplantation Society of Australia and New Zealand, on an Australian specific 'protocol' to be developed around patient eligibility criteria, logistical considerations, and post-transplant management.

Algorithms

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

Refer above- also added as ppt for editability in references.

Please see response earlier in Application Form for the question: *Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology.*

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