



Australian Government

Department of Health

Application 1703

Detection of minimal residual disease in patients with acute lymphoblastic leukaemia

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au

Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):

Corporation name: The Royal College of Pathologists of Australasia

ABN: REDACTED

Business trading name: The Royal College of Pathologists of Australasia

Primary contact name: REDACTED

Alternative contact numbers

Business: REDACTED

Mobile: REDACTED

Email: REDACTED

Alternative contact name: REDACTED

Alternative contact numbers

Business: REDACTED

Mobile: REDACTED

Email: REDACTED

2. (a) Are you a consultant acting on behalf on an applicant?

- Yes
 No

3. (a) Are you a lobbyist acting on behalf of an Applicant?

- Yes
 No

(b) If yes, are you listed on the Register of Lobbyists?

Not applicable

(c) Have you engaged a consultant on your behalf?

- Yes
 No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

4. Application title

Detection of minimal residual disease in patients with acute lymphoblastic leukaemia.

5. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

The detection of minimal residual disease (MRD) is feasible and relevant for many haematological malignancies such as non-Hodgkin lymphoma and myeloma; however, as clinical data is strongest for acute lymphoblastic leukaemia (ALL), this application will confine itself to ALL as the exemplar condition.

ALL can occur at any age, but most cases arise in children younger than 6 years of age, making ALL one of the most common types of childhood malignancy. ALL is a haematopoietic neoplasm of lymphoid precursors characterised by arrest of the differentiation process and, as a consequence, the abnormal clonal proliferation of immature (blast) cells. The majority of ALL have a B-cell lineage (80-85%), originating in the bone marrow, with the remaining 15-20% of cases having a T-cell lineage, originating most frequently in the thymus. B- and T-ALL are morphologically indistinguishable and can only be differentiated by immunophenotyping.^{1,2}

ALL patients may present with acute illness or with symptoms that develop slowly and persist for months. Typical symptoms include fever, fatigue, bone or joint pain, bleeding, anorexia, abdominal pain, and hepatosplenomegaly. B-ALL typically presents with cytopenia due to marrow involvement. Patients with T-ALL commonly present with a high white cell count due to blasts in the peripheral blood with anaemia and thrombocytopenia due to marrow replacement. In addition, a high proportion of T-ALL patients will develop an anterior mediastinal mass that may result in superior vena cava syndrome.^{1,2}

Although ALL is a highly aggressive malignant neoplasm that requires administration of intensive cytotoxic chemotherapy over years, 90% of treated children will survive. Initial morphological remission rates of 85-95% are similar in children and adults; however, for adults, 5-year survival is significantly reduced to only 30-40%, and even less in patients older than 60 years (10% have 3-year survival).^{1,3}

Given that most patients will achieve morphological remission it is important to identify factors that may predict a higher risk of relapse and allow stratification to more intensive therapy and haematopoietic stem cell transplantation (HSCT – also known as bone marrow transplantation(BMT)) as early as possible and as soon as remission has been obtained⁴ since long term outcomes on relapse, particularly in adult patients, remain extremely poor.⁵

Despite most patients achieving a morphological remission, many will still have persistent measurable minimal residual disease (MRD) which is the strongest predictor of relapse in ALL, regardless of treatment regimen.⁶

6. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

The primary clinical purpose for monitoring MRD is to determine the response to treatment and the risk of leukaemia relapse. MRD is the single most important prognostic marker in assessing ALL response in newly diagnosed and relapsed patients, and MRD results can be used to modify the intensity and duration of chemotherapy, or to use bone marrow transplant in first remission to prevent relapse.⁷

Patients with ALL who do not fully respond, or become resistant to therapy, as well as those patients who require longer treatment times to achieve remission, are likely to have residual disease that is not detectable by morphology^a. The detection of MRD by molecular or flow cytometry methods during or just

^a Post-treatment samples in “morphologic remission” could contain leukaemic cells ranging from less than 1 in 10,000–100,000 to 5% or more.⁸ Campana, D. (2012)

after treatment is therefore the most sensitive predictor of disease relapse, with MRD negativity associated with longer remissions and improved survival in ALL patients. By identifying patients at higher risk for relapse, the detection of MRD allows for additional treatments, as well as identifying those patients who may benefit from a bone marrow transplantation in first complete remission.⁸ MRD testing is considered standard of care in the management of ALL.

The three main methodologies used to detect and quantify residual tumour cells not detectable by morphology are multi-parametric flow cytometry of leukaemia-associated immunophenotypes and molecular methods including real-time quantitative qPCR and next-generation sequencing (NGS). Flow cytometry quantifies the number of cells present in a patient's sample (usually bone marrow aspirate but peripheral blood can be used) by measuring the signal emitted by fluorochrome-conjugated-specific monoclonal antibodies bound to antigens expressed on leukaemic cells. Flow cytometry analysis is rapid (results in less than one day) and although not as sensitive as molecular methods, it can still differentiate residual leukaemia cells from normal lymphoid precursors with a sensitivity of 10^{-3} -to 10^{-4} (one leukaemic cell out of 1,000–10,000 normal cells).⁹ Highly sensitive molecular methods (PCR or NGS), using cells obtained from either a bone marrow or blood, can detect leukaemic-associated immunoglobulin and T-cell receptor gene rearrangements using leukaemic-specific primers with a sensitivity of 1 in 100,000 cells.¹ PCR MRD results are usually available in 3 days. Molecular and flow cytometric methods are considered complementary as some individual ALL cases are technically easier to monitor using a molecular methodology or flow cytometry.

It should be noted that in May 2019, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended that the bispecific T cell engaging monoclonal antibody blinatumomab be listed on the PBS for patients with B-cell precursor ALL in haematological complete remission with MRD following induction chemotherapy. To be eligible, patients must have minimal residual disease defined as at least 10^{-4} (1 in 10,000 cells) blasts based on measurement in bone marrow, documented after an interval of at least 2 weeks from the last course of systemic chemotherapy given as intensive combination chemotherapy treatment of ALL or as subsequent salvage therapy, whichever was the later, and measured using PCR or flow cytometry.

7. (a) Is this a request for MBS funding?

- Yes
 No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

- Amendment to existing MBS item(s)
 New MBS item(s)

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

N/A

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

N/A

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

- i. A new item which also seeks to allow access to the MBS for a specific health practitioner group
- ii. A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
- iii. A new item for a specific single consultation item
- iv. A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

- Yes
 No

8. What is the type of service:

- Therapeutic medical service
- Investigative medical service
- Single consultation medical service
- Global consultation medical service
- Allied health service
- Co-dependent technology
- Hybrid health technology

9. For investigative services, advise the specific purpose of performing the service (which could be one or more of the following):

- i. To be used as a screening tool in asymptomatic populations
- ii. Assists in establishing a diagnosis in symptomatic patients
- iii. Provides information about prognosis
- iv. Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
- v. Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

10. Does your service rely on another medical product to achieve or to enhance its intended effect?

- Pharmaceutical / Biological
- Prosthesis or device
- No

11. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

N/A

(b) If yes, please list the relevant PBS item code(s):

N/A

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

N/A

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

N/A

12. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

N/A

(b) If yes, please provide the following information (where relevant):

N/A

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

N/A

(d) Are there any other sponsor(s) and/or manufacturer(s) that have a similar prosthesis or device component in the Australian marketplace that this application is relevant to?

N/A

13. Please identify any single and/or multi-use consumables delivered as part of the service?

Single use consumables: Laboratory consumables used for standard sequencing and flow cytometry.

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

The National Association of Testing Authorities (NATA) and the Royal College of Pathologists Australasia (RCPA) oversee the regulation of pathology testing for clinical purposes. Laboratories require accreditation by a joint NATA/RCPA process to ISO 15189, and specifically accredited to provide genetic testing. This accreditation process covers the technical aspects of the sample reception and processing, laboratory sequencing, analysis pipelines, curation (or interpretation) of results and production of the report to a clinical standard. It should be noted that the QA requirements are substantially different for MRD testing by flow or molecular techniques. There are no requirements for use of specific manufacturer's reagents, equipment or analysis pipelines.

Note: A non-commercial IVD is required to be regulated but not to be listed on the ARTG: testing using an IVD would be delivered only by Approved Practising Pathologists in NATA Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral only by registered Medical Practitioners (non-pathologists) in line with other tests in the MBS Pathology Table.

- 14. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:**

Type of therapeutic good: N/A

Manufacturer's name: N/A

Sponsor's name: N/A

- (b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?**

- Class III IVD
 AIMD
 N/A

- 15. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?**

- Yes (If yes, please provide supporting documentation as an attachment to this application form)
 No

- (b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?**

- Yes (if yes, please provide details below)
 No

ARTG listing, registration or inclusion number:

TGA approved indication(s), if applicable:

TGA approved purpose(s), if applicable:

- 16. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?**

- Yes (please provide details below)
 No

- 17. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?**

- Yes (please provide details below)
 No

PART 4 – SUMMARY OF EVIDENCE

18. Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
NCCN Guidelines USA (2021) ¹⁰	National Comprehensive Cancer Network (NCCN) Guidelines Acute Lymphoblastic Leukemia		https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1410
ESMO Clinical Practice Guidelines Europe (2016) ¹¹	Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up		https://pubmed.ncbi.nlm.nih.gov/27056999/
Paediatric studies			
Systematic review Prognosis Canada (2016) ¹²	Minimal Residual Disease Evaluation in Childhood Acute Lymphoblastic Leukemia: A Clinical Evidence Review	Identification of prognostic factors that allow risk stratification and tailored treatment have improved overall survival. Nearly a quarter of patients considered standard risk based on conventional prognostic factors still relapse, and relapse is associated with increased morbidity and mortality. Relapse is thought to result from extremely low levels of leukaemic cells left over once complete remission is reached, or MRD. This evidence review aimed to ascertain whether MRD is an independent prognostic factor for relapse and to assess the effect of MRD-directed treatment on patient-important outcomes in childhood ALL.	https://pubmed.ncbi.nlm.nih.gov/27099643/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
RCT UK (2013) ¹³	Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial	521 MRD low-risk patients were randomly assigned to receive one (n=260) or two (n=261) delayed intensification courses. No significant difference in event-free survival between the groups. The difference in 5-year EFS between the two groups was 1.1%. 11 patients given one delayed intensification and six (2.4%, 0.2-4.6) given two delayed intensifications relapsed (p=0.23). Three patients (1.2%, 0.2-6) given two delayed intensifications died of treatment-related causes compared with none in the group given one delayed intensification (p=0.08). Treatment reduction is feasible for children and young adults with ALL who are predicted to have a low risk of relapse based on rapid clearance of MRD by the end of induction therapy.	https://pubmed.ncbi.nlm.nih.gov/23395119/
RCT (newly diagnosed ALL) UK (2014) ¹⁴	Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial	533 MRD high-risk patients were randomly assigned to receive standard (n=266) or augmented (n=267) post-remission therapy. 5-year event-free survival was better in the augmented treatment group (89.6%) than in the standard group (82.8%; odds ratio 0.61, p=0.04). Overall survival at 5 years was higher, but not significant, in the augmented treatment group (92.9%) than in the standard therapy group (88.9%, OR 0.67, p=0.16). More adverse events occurred in the augmented treatment group than in the standard group.	https://pubmed.ncbi.nlm.nih.gov/24924991/
RCT Multicentre – Europe (2021) ¹⁵	Effect of Blinatumomab vs Chemotherapy on Event-Free Survival Among Children With High-risk First-Relapse B-Cell Acute Lymphoblastic Leukemia	Patients with high-risk first-relapse B-ALL in morphologic complete remission (M1 marrow, <5% blasts) or with M2 marrow (blasts ≥5% and <25%) were randomised to receive 1 cycle of blinatumomab (n = 54; 15 µg/m ² /d for 4 weeks, continuous intravenous infusion) or standard chemotherapy (n = 54) for the third consolidation. Treatment with blinatumomab compared with chemotherapy for consolidation treatment resulted in a statistically significant hazard ratio for event-free survival of 0.33 after a median of 22.4 months of follow-up.	https://pubmed.ncbi.nlm.nih.gov/33651091/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
RCT United Kingdom, Australia, New Zealand (2010) ¹⁶	Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial	216 children stratified into high-, intermediate-, and standard-risk groups based on duration of first complete remission, site of relapse, and immunophenotype were randomly assigned to either idarubicin or mitoxantrone. After three blocks of therapy, all high-risk patients and those intermediate-risk with post-induction high MRD $\geq 10^{-4}$ received an allogeneic stem-cell transplant. Standard-risk and intermediate-risk patients with post-induction low MRD $< 10^{-4}$ cells) continued chemotherapy. Estimated 3-year progression-free survival was 35.9% in the idarubicin group versus 64.6% in the mitoxantrone group ($p=0.0004$), and 3-year overall survival was 45.2% versus 69.0% ($p=0.004$). Differences in progression-free survival between groups were mainly related to a decrease in disease events (progression, second relapse, disease-related deaths; HR 0.56, $p=0.007$) rather than an increase in adverse treatment effects (treatment death, second malignancy; HR 0.52, $p=0.11$).	https://pubmed.ncbi.nlm.nih.gov/21131038/
Comparative Level III-2 prognostic study China (2019) ¹⁷	Minimal Residual Disease-guided Risk Restratification and Therapy Improves the Survival of Childhood Acute Lymphoblastic Leukemia: Experience From a Tertiary Children's Hospital in China	676 children with ALL were enrolled. In the predictive study group, 476 patients were enrolled with 5-year cumulative incidence of relapse rates of the low-risk (LR), intermediate-risk (IR), and high-risk groups being 11.0%, 12.6%, and 32.7%, respectively. In the intervention study group, patients enrolled were reclassified into risk groups according to the MRD levels. The 3-year event-free survival and overall survival were 85.2% and 90.6%, respectively, higher than the predictive group (79.1% and 84.7%, respectively; $p<0.05$). The 3-year cumulative incidence of relapse in the LR and IR groups of the intervention group were significantly lower than those in the predictive group ($p<0.05$). The risk of relapse in the LR and IR groups can be significantly reduced after MRD-guided risk re-stratification.	https://pubmed.ncbi.nlm.nih.gov/30640823/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
Comparative Level II prognostic study Germany (2019) ¹⁸	Results of CoALL 07-03 study childhood ALL based on combined risk assessment by in vivo and in vitro pharmacosensitivity	In a 2-step stratification, 773 children with acute lymphoblastic leukemia were allocated to receive either low- or high-risk treatment, based on initial white blood cell count, age, and immunophenotype. A second stratification was performed according to the results of in vitro pharmacosensitivity toward prednisolone, vincristine, and asparaginase (PVA score) and in vivo response after induction therapy (MRD). Therapy was reduced for both risk groups in patients with a low PVA score or negative MRD result, and intensified in patients with a high PVA score. Study concluded that chemotherapy could be reduced in children with ALL selected by stringent in vivo measurement of MRD without jeopardising overall outcomes.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6880907/
Retrospective cohort (before and after) study Level III-3 prognostic study Italy (2018) ¹⁹	Pre- and post-transplant minimal residual disease predicts relapse occurrence in children with acute lymphoblastic leukaemia	Retrospective before and after in 119 children in complete remission who had undergone stem cell transplantation. MRD was measured by PCR in bone marrow samples collected pre-HSCT and during the first and third trimesters after HSCT. The overall event-free survival (EFS) was 50%. The cumulative incidence of relapse and non-relapse mortality was 41% and 9%. Any degree of detectable pre-HSCT MRD was associated with poor outcome: EFS was 39% and 18% in patients with MRD positivity $<1 \times 10^{-3}$ and $\geq 1 \times 10^{-3}$, respectively, versus 73% in MRD-negative patients ($P < 0.001$). Low-level MRD had a very strong negative impact only in patients transplanted in second or further CR. MRD after HSCT enabled patients to be stratified, with increasing MRD between post-HSCT1 and post-HSCT3 clearly defining cohorts with a different outcome.	https://pubmed.ncbi.nlm.nih.gov/29359790/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
<p>Prospective cohort (before and after) study</p> <p>Level III-3 prognostic study France (2014)²⁰</p>	<p>Clinical value of pre-transplant minimal residual disease in childhood lymphoblastic leukaemia: the results of the French minimal residual disease-guided protocol</p>	<p>MRD is a major predictive factor of the cure rate of ALL. Haematopoietic cell transplantation is a treatment option for patients at high risk of relapse. A prospective study evaluated the feasibility and efficacy of the reduction of immunosuppressive medication after transplantation. Immunoglobulin (Ig)H/T-cell receptor MRD 30 d before transplant was obtained in 122/133 high-risk paediatric ALL patients. Only remission status differed (first or second complete remission) between those with MRD $<10^{-3}$ (n=95) and MRD $\geq 10^{-3}$ (n=27). Multivariate analysis identified sex match and MRD as being significantly associated with 5-year survival. MRD $\geq 10^{-3}$ compromised the 5-year cumulative incidence of relapse (43.6 vs. 16.7%). Complete remission status and stem cell source did not modify the relationship between MRD and prognosis. Pre-transplant MRD is a major predictor of outcome for ALL. The MRD-guided strategy resulted in survival for 72.3% of patients with MRD $<10^{-3}$ and 40.4% of those with MRD $\geq 10^{-3}$.</p>	<p>https://pubmed.ncbi.nlm.nih.gov/24479958/</p>
<p>Cohort</p> <p>Prognostic</p> <p>Germany (2015)²¹</p>	<p>Monitoring of minimal residual disease after allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia allows for the identification of impending relapse: results of the ALL-BFM-SCT 2003 trial</p>	<p>359 children with relapsed ALL received allogeneic SCT. 113 of these patients, had MRD tested at days +30, +60, +90, +180, and +365 after transplantation. All patients showed a 3-year probability of event-free survival (pEFS) of 55%. The cumulative incidence rates of relapse and treatment-related mortality were 32% and 12%, respectively. The pEFS was 60% for patients who received their transplantations in second complete remission, 50% for patients in \geq third complete remission, and 0% for patients not in remission (p = .015). At all time points, the level of MRD was inversely correlated with event-free survival (EFS; p < .004) and positively correlated with the cumulative incidence of relapse (p < .01). MRD after transplantation was a reliable marker for predicting impending relapses and could thus serve as the basis for pre-emptive therapy.</p>	<p>https://pubmed.ncbi.nlm.nih.gov/25605857/</p>

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
Cohort Prognostic Multicentre USA, Australia and New Zealand (2020) ²²	Outcome in Children With Standard-Risk B-Cell Acute Lymphoblastic Leukemia: Results of Children's Oncology Group Trial AALL0331	<p>5,377 ALL patients received a 3-drug induction with dexamethasone, vincristine, and pegaspargase (PEG) and were classified as SR low, SR average, or SR high. Patients with SR-average disease were randomly assigned to receive either standard 4-week consolidation (SC) or 8-week intensified consolidation (IC). Those with SR-high disease were non-randomly assigned to the full COG-augmented BFM regimen, including 2 interim maintenance and delayed intensification phases. The 6-year EFS rate for all patients was 88.96% ± 0.46%, and overall survival (OS) was 95.54% ± 0.31%. SR-average patients: the 6-year continuous complete remission (CCR) and OS rates for SC versus IC were 87.8% ± 1.3% vs 89.1% ± 1.2% (p = 0.52) and 95.8% ± 0.8% vs 95.2% ± 0.8% (p = 1.0), respectively. Those with SR-average disease with end-induction MRD of 0.01% to < 0.1% had an inferior outcome compared with those with lower MRD and no improvement with IC (6-year CCR: SC, 77.5% ± 4.8%; IC, 77.1% ± 4.8%; P = .71). At 6 years, the CCR and OS rates among 635 non-randomly treated patients with SR-high disease were 85.55% ± 1.49% and 92.97% ± 1.08%, respectively. The addition of IC to treatment for patients with SR-average disease did not improve CCR or OS, even in patients with higher MRD, in whom it might have been predicted to provide more value. The EFS and OS rates are excellent for this group of patients with SR ALL, with particularly good outcomes for those with SR-high disease.</p>	https://pubmed.ncbi.nlm.nih.gov/31825704/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
Comparative cohort UK (2017) ²³	Use of Minimal Residual Disease Assessment to Redefine Induction Failure in Pediatric Acute Lymphoblastic Leukemia	3,113 paediatric patients with MRD measured by RQ-PCR with a median follow-up of 5 years 9 months. Fifty-nine patients (1.9%) had morphologic induction failure with 5-year event-free survival (EFS) of 50.7% and 5-year overall survival of 57.7%. Of these, a small proportion of patients with M2 marrow (6 of 44) and a low EOI MRD level (, 0.01%) had 5-year EFS of 100%. Conversely, among patients with morphologic remission 2.3% (61 of 2,633) had high MRD ($\geq 5\%$) and 5-year EFS of 47.0%, which was similar to those with morphologic induction failure. Redefining induction failure to include morphologic induction failure and/or MRD $\geq 5\%$ identified 3.9% (120 of 3,133 patients) of the trial cohort with 5-year EFS of 48.0%. Induction failure (morphologic or MRD $\geq 5\%$) occurred most frequently in T-ALL (10.1%; 39 of 386 T-ALL cases) and B-other ALL, that is, lacking established chromosomal abnormalities (5.6%; 43 of 772 B-other cases).	https://pubmed.ncbi.nlm.nih.gov/28045622/
Comparative study with historical controls Level III-3 intervention evidence Netherlands (2016) ²⁴	Successful Therapy Reduction and Intensification for Childhood Acute Lymphoblastic Leukemia Based on Minimal Residual Disease Monitoring: Study ALL10 From the Dutch Childhood Oncology Group	778 paediatric patients stratified on the basis of MRD levels after the first and second course of chemotherapy. Therapy was substantially reduced in patients with undetectable MRD (standard risk) and intensified in patients with intermediate (medium risk) and high (high risk) levels of MRD. In MRD-based standard-risk patients, the 5-year EFS rate was 93%, the 5-year survival rate was 99%, and the 5-year cumulative incidence of relapse rate was 6%. MRD-based medium-risk patients had a significantly higher 5-year EFS rate (88% with therapy intensification (including 30 weeks of asparaginase exposure and dexamethasone/vincristine pulses) compared with historical controls (76%). Intensive chemotherapy and stem cell transplantation in MRD-based high-risk patients resulted in a significantly better 5-year EFS rate (78% v 16% in controls). Overall outcome improved significantly (5-year EFS rate 87%, 5-year survival rate 92%, and 5-year cumulative incidence of relapse rate 8%) compared with preceding Dutch Childhood Oncology Group protocols.	https://pubmed.ncbi.nlm.nih.gov/27269950/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
RCT (newly diagnosed ALL) Europe - AIEOP-BFM 2000 (2010) ²⁵	Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study	The AIEOP-BFM ALL 2000 study introduced standardized quantitative assessment of MRD based on immunoglobulin and T-cell receptor gene rearrangements as PCR-MRD, at 2 time points (TPs), to stratify patients in a large prospective study. Patients with precursor B (pB) ALL (n = 3,184) were considered MRD standard risk (MRD-SR) if MRD was already negative at day 33 (analysed by 2 markers, with a sensitivity of at least 10 ⁻⁴); MRD high risk (MRD-HR) if ≥10 ⁻³ at day 78 and MRD intermediate risk (MRD-IR): others. MRD-SR patients were 42% (1,348): 5-year event-free survival (EFS) is 92.3%. Fifty-two percent (1,647) were MRD-IR: EFS 77.6%. Six percent of patients (189) were MRD-HR: EFS 50.1% (p < .001). PCR-MRD discriminated prognosis even on top of white blood cell count, age, early response to prednisone, and genotype. MRD response detected by sensitive quantitative PCR at 2 predefined TPs is highly predictive for relapse in childhood pB-ALL.	https://pubmed.ncbi.nlm.nih.gov/20154213/
RCT (Newly diagnosed ALL) Europe - AIEOP-BFM (2011) ²⁶	Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study	The prognostic value of MRD in large series of childhood T-ALL has not yet been established. Patients were considered MRD standard risk (MRD-SR) if MRD was negative at day 33 (time point 1 [TP1]) and day 78 (TP2), analysed by at least 2 sensitive markers; MRD intermediate risk (MRD-IR) if positive either at day 33 or 78 and < 10 ⁻³ at day 78; and MRD high risk (MRD-HR) if ≥ 10 ⁻³ at day 78. A total of 464 patients with T-ALL were stratified by MRD: 16% of them were MRD-SR, 63% MRD-IR, and 21% MRD-HR. Their 7-year event-free-survival (SE) was 91.1% (3.5%), 80.6% (2.3%), and 49.8% (5.1%) (p < .001), respectively. Negativity of MRD at TP1 was the most favourable prognostic factor. An excellent outcome was also obtained in 32% of patients turning MRD negative only at TP2, indicating that early (TP1) MRD levels were irrelevant if MRD at TP2 was negative (48% of all patients). MRD ≥ 10 ⁻³ at TP2 constitutes the most important predictive factor for relapse in childhood T-ALL.	https://pubmed.ncbi.nlm.nih.gov/21719599/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
Case series Australia (2021) ²⁷	Outcomes for Australian children with relapsed/refractory acute lymphoblastic leukaemia treated with blinatumomab	24 children with relapsed/refractory precursor B-cell acute lymphoblastic leukaemia (BALL) treated with blinatumomab. Resulting in a MRD response rate of 58%, 2-year progression-free survival of 39% and 2-year overall survival of 63%. In total, 83% (n = 20/24) proceeded to haematopoietic stem cell transplant, directly after blinatumomab (n = 12) or following additional salvage therapy (n = 8). Four patients successfully received CD19-directed chimeric antigen receptor T-cell therapy despite prior blinatumomab exposure. Inferior 2-year PFS was associated with MRD positivity (20%, n = 15) and in KMT2A-rearranged infants (15%, n = 9).	https://pubmed.ncbi.nlm.nih.gov/33638292/
Prospective cohort series Australia and Netherlands (2013) ⁷	High-risk childhood acute lymphoblastic leukemia in first remission treated with novel intensive chemotherapy and allogeneic transplantation	Children with ALL and high MRD levels after initial chemotherapy have a poor clinical outcome. 91/111 high risk patients began HR treatment blocks, with 79 completing the protocol (3 remission failures, 12 relapses, 7 toxic deaths in remission and 10 patients who changed protocol due to toxicity or clinician/parent preference). For the 111 HR patients, 5-year event-free survival was 66.8% (±5.5) and overall survival was 75.6% (±4.3). The 30 patients treated as HR solely on the basis of high MRD levels had a 5-year EFS of 63% (±9.4%).	https://pubmed.ncbi.nlm.nih.gov/23407458/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
Retrospective case series Germany (2009) ²⁸	Prognostic value of minimal residual disease quantification before allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia: the ALL-REZ BFM Study Group	MRD before allogeneic stem-cell transplantation predicts outcome in children with relapsed ALL. 91 children with relapsed ALL received stem-cell transplantation in \geq second remission were enrolled. MRD quantification was performed by RT-PCR. Probability of event-free survival (pEFS) and cumulative incidence of relapse (CIR) in 45 patients with MRD $\geq 10^{-4}$ leukemic cells was 0.27 and 0.57 compared with 0.60 and 0.13 in 46 patients with MRD $< 10^{-4}$ leukemic cells (EFS, $p = .004$; CIR, $p < .001$). Intermediate-risk patients with MRD $\geq 10^{-4}$ leukemic cells ($n = 14$) had a pEFS of 0.20 and CIR of 0.73, whereas patients with MRD $< 10^{-4}$ leukemic cells ($n = 21$) had a pEFS of 0.68 and CIR of 0.09 (EFS, $p = .020$; CIR, $p < .001$). High-risk patients who received transplantation with an MRD load of $< 10^{-4}$ leukemic cells ($n = 25$) showed a pEFS and CIR of 0.53 and 0.18, respectively. In contrast, pEFS and CIR were 0.30 and 0.50 in patients who received transplantation with an MRD load of $\geq 10^{-4}$ leukemic cells. Multivariate Cox regression analysis revealed MRD as the only independent parameter predictive for EFS ($p = .006$). MRD is an important predictor for post-transplantation outcome.	https://pubmed.ncbi.nlm.nih.gov/19064980/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
Comparative study with historical controls Germany (2013) ²⁹	Use of allogeneic hematopoietic stem-cell transplantation based on minimal residual disease response improves outcomes for children with relapsed acute lymphoblastic leukemia in the intermediate-risk group	ALL patients with an MRD level of $\geq 10^{-3}$ (n = 99) at the end of induction therapy were allocated to HSCT. Those with an MRD level $<10^{-3}$ (n = 109) continued to receive chemotherapy. The probability of event-free survival for patients with MRD $\geq 10^{-3}$ was $64\% \pm 5\%$ in this study compared with $18\% \pm 7\%$ in the predecessor study ($p < .001$). This was achieved by reducing the cumulative incidence of subsequent relapse at 8 years from $59\% \pm 9\%$ to $27\% \pm 5\%$ ($p < .001$). The favourable prognosis of patients with MRD $< 10^{-3}$ could be confirmed in those with a late combined or isolated bone marrow B-cell precursor (BCP) –ALL relapse (CIR, $20\% \pm 5\%$), whereas patients with an early combined BCP-ALL relapse had an unfavourable outcome (CIR, $63\% \pm 13\%$; $p < .001$). Allogeneic HSCT markedly improved the prognosis of patients with intermediate risk of relapse of ALL and unsatisfactory MRD response. As a result, outcomes in this group approximated those of patients with favourable MRD response. Patients with early combined relapse require treatment intensification even in case of favourable MRD response, demonstrating the prognostic impact of time to relapse.	https://pubmed.ncbi.nlm.nih.gov/23775972/
Adult studies			
Systematic review and meta-analysis (2019) ³⁰	A systematic literature review and meta-analysis of minimal residual disease as a prognostic indicator in adult B-cell acute lymphoblastic leukemia	A systematic literature review and meta-analysis were performed to elucidate the clinical significance of MRD with respect to relapse-free survival and overall survival in precursor B-cell acute lymphoblastic leukaemia. The primary analysis revealed improved relapse-free survival across all studies for patients who achieved MRD negativity. Improved overall survival for patients who achieved MRD negativity was also observed (hazard ratio, 2.19). Despite heterogeneity in study design and patient populations between the contributing studies, these data provide a compelling argument for MRD as a clinical tool for assessing prognosis and guiding treatment decisions in precursor B-cell acute lymphoblastic leukaemia.	https://pubmed.ncbi.nlm.nih.gov/30890593/

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
<p>Prospective single arm clinical trial (newly diagnosed ALL – ALLG ALL06 Study)</p> <p>Australia (2021)³¹</p>	<p>An MRD stratified pediatric protocol is as deliverable in adolescents and young adults as children with ALL</p>	<p>MRD response stratified patients to HR treatment and transplantation in 82 patients (median age 22 years). Median follow up of 44 (1-96) months, estimated 3-year DFS was 72.8% and estimated 3-year overall survival was 74.9%. End induction/consolidation MRD negativity rate was 58.6%. Body mass index ≥ 30 and day 79 MRD positivity were associated with poorer DFS and OS. TP2 MRD neg was associated with improved 3-year DFS of 84.5% versus 57.9% and improved 3-year OS of 91.9% versus 61.9% in patients who had any level of TP2 MRD positivity. For those proceeding to SCT in CR1 according to study protocol, 3 yr DFS and OS was 75%.</p>	<p>Accepted for publication in Blood Advances</p>
<p>Comparative study with historical controls</p> <p>Level III-3 intervention study</p> <p>China (2016)³², 2019 correction³³</p>	<p>Minimal residual disease- and graft-vs.-host disease-guided multiple consolidation chemotherapy and donor lymphocyte infusion prevent second acute leukemia relapse after allotransplant</p>	<p>Forty-seven subjects with acute leukemia relapsing after an allotransplant and who achieved complete remission after post-relapse induction chemotherapy and DLI were eligible. The use of consolidation chemotherapy and DLI was guided by the results of MRD testing and whether or not DLI caused acute and/or chronic GvHD. Outcomes were compared with those of 34 similar historical controls who did not receive consolidation chemotherapy and DLIs after induction chemotherapy and DLI.</p>	<p>https://pubmed.ncbi.nlm.nih.gov/27629395/</p>
<p>Retrospective cohort study</p> <p>Level III-3 prognostic study</p> <p>China (2021)³⁴</p>	<p>Minimal residual disease level determined by flow cytometry provides reliable risk stratification in adults with T-cell acute lymphoblastic leukaemia</p>	<p>The prognostic value of multiparameter flow cytometry (FCM)-based MRD at the end of induction (EOI-MRD) was evaluated in 94 adult patients with T-ALL. MRD was detected by six- to eight-colour FCM. Patients who were EOI-MRD positive had a higher cumulative incidence of relapse (CIR) (87.6% vs. 38.8%, $p = 0.0020$), and a lower relapse-free survival (RFS) (5.4% vs. 61.0%, $p = 0.0005$) and overall survival (OS) (32.7% vs. 69.7%, $p < 0.0001$) compared to EOI-MRD negative. Patients who received allogeneic haematopoietic stem cell transplantation (allo-HSCT) at their first remission, EOI-MRD positivity was predictive of post-transplant relapse (2-year CIR: 68.2% vs. 4.0%, $p = 0.0003$). EOI-MRD is an independent prognostic factor for CIR (HR 2.139, $p = 0.046$), RFS (HR 2.125, $p = 0.048$) and OS (HR 2.987, $p = 0.017$).</p>	<p>https://pubmed.ncbi.nlm.nih.gov/33764511/</p>
<p>Mixed adult and paediatric</p>			

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research
Meta-analysis (2017) ³⁵	Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis	39 publications (n= 13 637 patients): 16 adult studies (2,076 patients), 20 paediatric (11, 249 patients), and 3 mixed (312 patients). The event-free survival hazard ratio (HR) for achieving MRD negativity is 0.23 for paediatric patients and 0.28 for adults. The respective HRs for overall survival are 0.28 and 0.28. The effect was similar across all subgroups and covariates. The value of having achieved MRD negativity is substantial in both paediatric and adult patients with ALL. These results are consistent across therapies, methods of and times of MRD assessment, cut-off levels, and disease subtypes. MRD status warrants consideration as an early measure of disease response for evaluating new therapies, improving the efficiency of clinical trials, accelerating drug development, and for regulatory approval.	https://pubmed.ncbi.nlm.nih.gov/28494052/
RCT Multicentre: US, Canada, Australia, and New Zealand (2021) ³⁶	Effect of Postreinduction Therapy Consolidation With Blinatumomab vs Chemotherapy on Disease-Free Survival in Children, Adolescents, and Young Adults With First Relapse of B-Cell Acute Lymphoblastic Leukemia	Standard chemotherapy for first relapse of B-cell acute lymphoblastic leukemia (B-ALL) in children, adolescents, and young adults is associated with high rates of severe toxicities, subsequent relapse, and death, especially for patients with early relapse (high risk) or late relapse with residual disease after reinduction chemotherapy (intermediate risk). Following reinduction, individuals in the high- and intermediate-risk group were randomised in a 1:1 ratio to receive blinatumomab (experimental, n=105) or standard chemotherapy (control, n=103). With 2.9 years of median follow-up, 2-year disease-free survival was 54.4%for the blinatumomab group vs 39.0%for the chemotherapy group (HR for disease progression or mortality, 0.70). Two-year overall survival was 71.3%for the blinatumomab group vs 58.4%for the chemotherapy group (HR for mortality, 0.62).	https://pubmed.ncbi.nlm.nih.gov/33651090/

19. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). Please do not attach full text articles, this is just intended to be a summary.

	Type of study design	Title of research	Short description of research	Website link to research	Date
Paediatric – most clinical trials currently recruiting (>30) describe the use of a drug to achieve remission in MRD-positive patients					
1.	Single arm, interventional USA N=32	Inotuzumab Ozogamicin for Children With MRD Positive CD22+ Lymphoblastic Leukemia	Some patients with newly diagnosed ALL maintain low levels of MRD, despite achieving complete remission with less than 5% blasts in the bone marrow. Others experience re-emergence of low level MRD or increasing levels of MRD on therapy or post-transplant. Inotuzumab ozogamicin is an antibody-drug conjugate composed of a humanised IgG subtype 4 monoclonal CD22-targeted antibody linked to calicheamicin, a potent anti-tumour antibiotic. CD22 is expressed in more than 90% of patients with B-cell ALL, making it a good target in this patient population. Inotuzumab ozogamicin has demonstrated exceptional activity in adults with relapsed or refractory B-ALL.	NCT03913559	Estimated study completion date January 2024
2.	Comparative, non-randomised USA N=95	The EndRAD Trial: Eliminating Total Body Irradiation (TBI) for NGS-MRD Negative Children, Adolescents, and Young Adults With B-ALL	This study will evaluate the use of non- TBI (total body irradiation) conditioning for B-ALL patients with low risk of relapse as defined by absence of NGS-MRD (next generation sequencing minimal residual disease) before receiving a hematopoietic cell transplant (HCT). Patients diagnosed with B-ALL who are candidates for HCT will be screened by NGS-MRD on a test of bone marrow done before the HCT. Subjects who are pre-HCT NGS-MRD negative will be eligible to receive a non-TBI conditioning regimen as part of the treatment cohort of the study.	NCT03509961	Estimated study completion date April 2022

	Type of study design	Title of research	Short description of research	Website link to research	Date
3.	Single arm, interventional USA N=35	Blinatumomab Bridging Therapy	Testing the ability of a biologically active therapy in blinatumomab, an anti-CD19/CD3 bispecific T-cell engager, to further reduce residual leukemia immediately prior to HCT to improve post-HCT outcomes. This Phase 2 study will determine the effectiveness of delivering 1 to 2 cycles of blinatumomab (Days 1-28) as bridging therapy in children, adolescent and young adults with relapse or persistent MRD B-ALL.	NCT04556084	Estimated study completion date October 2024
4.	Single arm, interventional China N=20	Anti-CD19 CAR-T Therapy Combine With HSCT to Treat MRD+ B-cell Malignancies	For micro residual disease (MRD) positive patients who have undergone at least 2 cycles chemotherapies for their CD19+ B-cell malignancies, there would be much more risks for them to receive haematological stem cell transplantation (HSCT) than MRD- patients. In order to reduce HSCT-related adverse events for these patients, investigators plan to conduct CAR-T therapies on them first to make them achieve MRD- statuses, and then transfer them to HSCT.	NCT03366324	Estimated study completion date June 2021
5.	Single arm, interventional China N=100	Study of Sequential CAR-T Cell Treating Leukemia Children	A phase II clinical trial of sequential chimeric antigen receptor T cell targeting at different B-cell antigens in refractory or relapsed B-cell acute lymphoblastic leukemia children. Participants will be eligible if they are heavily treated B-ALL who failed from re-induction chemotherapy after relapse or continued MRD+ for more than three months, and had positive CD19 and CD22 expressions on leukemia blasts by FCM (>95% CD19 and >95% CD22). After CAR T-cell infusion, clinical outcomes including overall survival (OS), disease-free survival (DFS), adverse effects and relapse will be evaluated.	NCT04340154	Estimated study completion date November 2022

	Type of study design	Title of research	Short description of research	Website link to research	Date
Adult - most clinical trials currently recruiting (>60) describe the use of a drug to achieve remission in MRD-positive patients					
6.	Comparative, non-randomised Italy N=76	Feasibility and Effectiveness of Inotuzumab Ozogamicin in B-Cell Acute Lymphoblastic Leukemia (ALL2418)	Phase 2A exploratory study of feasibility and effectiveness of Inotuzumab Ozagomicin in adult patients with ALL with positive minimal residual disease before any hematopoietic stem cell transplantation. The study is divided in two cohorts; cohort 1 will enrol 38 Ph+ patients, cohort 2 will enrol 38 Ph- patients. Outcomes: Number of patients obtaining a negative MRD and overall survival.	NCT03610438	Estimated study completion date November 2022
7.	Single arm, interventional China N=10	Anti-CD19/CD22 Bispecific CAR-T Cell Therapy for MRD Positive ALL	Administration with anti-CD19/ CD22 CAR-T cells in the MRD-positive ALL patients. Outcomes: MRD clearance and overall survival.	NCT03919526	Estimated study completion date June 2021
8	Single arm, interventional Germany N=80	Blinatumomab in Adult Patients With Minimal Residual Disease (MRD) of B-precursor Acute Lymphoblastic Leukemia	This study is designed to confirm the efficacy, safety, and tolerability of blinatumomab in patients with MRD of B-precursor ALL in complete haematological remission including patients with relapse after SCT. Outcomes: MRD status, remission, relapse, overall survival.	NCT03109093	Estimated study completion date January 2023
9	Single arm, interventional China N=20	Anti-CD19 CAR-T Therapy Combine With HSCT to Treat MRD+ B-cell Malignancies	A Phase 1/2 Study Evaluating the Safety and Efficacy of the Combination of Anti-CD19 Chimeric Antigen Receptor-Modified T Cell (CAR-T) Therapy and Hematological Stem Cell Transplantation (HSCT) for MRD+ B-cell Malignancies	NCT03366324	Estimated study completion date June 2021

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

- 20. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):**

Royal College of Pathologists of Australasia

- 21. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):**

Australasian Leukaemia & Lymphoma Group (ALLG)

Haematology Society of Australia & New Zealand (HSANZ)

The Australian and New Zealand Children's Haematology/Oncology Group (ANZCHOG)

- 22. List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):**

Leukaemia Foundation and the Blood Cancer Taskforce

Kids' Cancer Project

Canteen

- 23. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:**

N/A

- 24. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):**

Name of expert 1: REDACTED

Telephone number(s): REDACTED

Email address: REDACTED

Justification of expertise: REDACTED

Name of expert 2: REDACTED

Telephone number(s): REDACTED

Email address: REDACTED

Justification of expertise: REDACTED

Name of expert 3: REDACTED

Telephone number(s): REDACTED

Email address: REDACTED

Justification of expertise: REDACTED

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

25. Define the medical condition, including providing information on the natural history of the condition and a high-level summary of associated burden of disease in terms of both morbidity and mortality:

Acute lymphocytic leukaemia (ALL) is a malignancy of B or T lymphoblasts that is characterised by the uncontrolled differentiation and proliferation of abnormal, immature lymphocytes and their progenitors within the bone marrow, blood, and extramedullary sites.³⁷

ALL patients may present with acute illness or with non-specific symptoms that develop slowly and persist for months. Common symptoms include fever, fatigue, bone or joint pain, easy or spontaneous bruising/bleeding, unintentional weight loss or anorexia, abdominal pain, and infections. Hepatosplenomegaly is observed in up to half of adults on presentation, caused by the sequestration of malignant lymphoblasts in the spleen and liver.³⁷ B-ALL typically presents with cytopenia due to bone marrow involvement. Patients with T-ALL commonly present with a high white cell count due to blasts in the peripheral blood with anaemia and thrombocytopenia due to marrow replacement. In addition, a high proportion of T-ALL patients will develop an anterior mediastinal mass that may result in superior vena cava syndrome.^{1,2} A small number of patients ($\approx 10\%$) may experience central nervous system (CNS) involvement.³⁸

The incidence of ALL is bimodal, with a peak occurring in very young patients (aged 2 to 10 years) with a second, smaller peak occurring in adults aged greater than 50 years.^{37,39} Half of all ALL cases are paediatric patients less than 15 years old. In Australia, the number of new ALL cases per year is relatively low compared to other cancers, with an estimated age-standardised incidence rate of 1.7 cases per 100,000 persons in 2020. As can be seen in Figure 1, the peak incidence of ALL occurs in the 0-4 years age bracket with 6.1 cases per 100,000. Incidence is slightly higher in males compared to females (1.5 vs 2.0 per 100,000), and this difference is evident in all age groups.⁴⁰ Despite being a highly aggressive malignant neoplasm, ALL has an overall 5-year survival rate of 74.1 per cent (Table 1). This is a result of very low mortality rates in young patients, with close to 90% of treated children surviving, compared to more devastating disease in adults, who experience a significantly higher rate of mortality (Figure 1) and a reduced 5-year survival of only 30-40% in patients older than 60 years.^{1,3,37,39}

For adults, criteria for a good ALL prognosis include:

- age < 30 years;
- no abnormal cytogenetics;
- white blood cell count < 30,000;
- complete remission within 4 weeks; and
- low or undetectable MRD at end of induction.

For adults, poor prognostic factors include:

- age > 60 years;
- abnormal cytogenetics - t(9:22), t(4:11);
- failure to achieve remission within 4 weeks;
- precursor B-cells > 100,000;³⁷ and
- persistence or recurrence of MRD at any time point.

For children, criteria for a good prognosis ALL include:

- age: greater than 1 year and under 10 years of age;
- white blood cell count < 50,000;
- presence of low-risk cytogenetics - t(12;21); hyperdiploidy; and

- low or undetectable MRD at end of induction.

For children, poor prognostic factors include:

- infant ALL (age <12 months);
- age over 10 years of age;
- white blood cell count > 50,000;
- presence of high risk cytogenetics - t(9:22), t(4:11); t(17;19); hypodiploidy;
- failure to achieve a morphologic remission at the end of induction therapy;
- high levels of MRD at end induction and ongoing high MRD despite subsequent courses of treatment; and
- the presence of specific microdeletions and detectable MRD after induction chemotherapy (IKZF1^{plus}) patients.

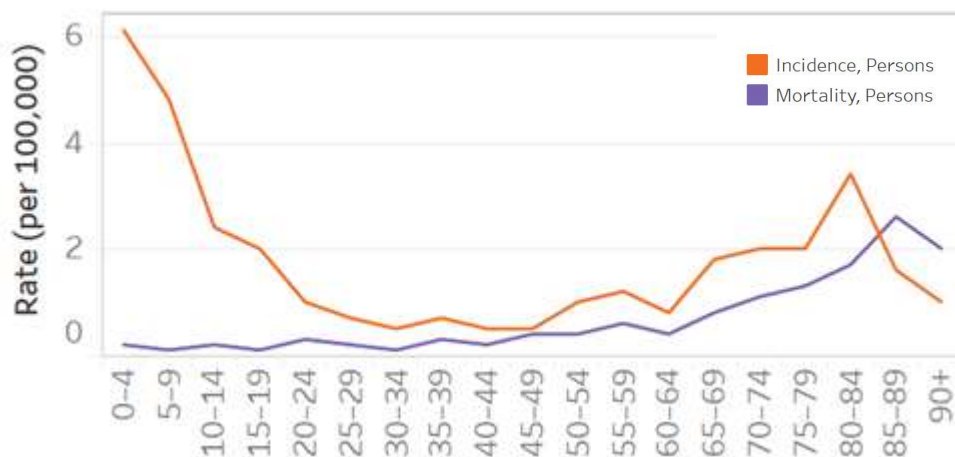


Figure 1 Estimated age-specific rates of acute lymphoblastic leukaemia in Australia, 2020³⁹

Table 1 Incidence (2015), mortality (2016) and 5-year relative survival (2011–2015) of ALL⁴¹

Cancer type (ICD-10 code)	Incidence		Mortality		Relative survival (%)
	Number	ASR	Number	ASR	
Acute lymphoblastic leukaemia (C91.0)	389	1.6	97	0.4	74.0

ASR = age standardised rate

26. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of 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 service:

Patients presenting with clinical features suspicious of a haematological malignancy (fever, fatigue, bone or joint pain, easy or spontaneous bruising/bleeding, unintentional weight loss or anorexia, abdominal pain, and infections) such as ALL would typically undergo investigations by their primary health care provider including full blood count and other basic laboratory investigations including electrolytes, renal panel, and levels of lactate dehydrogenase. If the results of these investigations are consistent with ALL, patients are typically referred to a specialist haematologist physician for further investigations, which may include further laboratory investigations (immunophenotyping of peripheral blood, cytological/histopathological examination of bone marrow biopsy/lymph nodes), radiological investigations and/or diagnostic procedures (bone marrow biopsy, biopsy of lymph nodes/affected organs). Lumbar puncture may be used to evaluate CNS involvement, with the cerebrospinal fluid checked for the presence of lymphoblasts.³⁷

The US National Comprehensive Cancer Network's diagnosis guidelines for patient samples with $\geq 20\%$ bone marrow lymphoblasts should undergo:

- morphologic assessment of Wright-Giemsa-stained bone marrow aspirate smears;
- haematoxylin and eosin-stained core biopsy and clot sections;
- comprehensive flow cytometric immunophenotyping;
- baseline flow cytometric and/or molecular characterisation of leukaemic clone to facilitate subsequent MRD analysis; and
- karyotyping of G-banded metaphase chromosome.^{10, 37}

27. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

If ALL is diagnosed^b using the investigations described in Q25, then diagnostic testing would cease, and the patient would commence treatment, with most treatment protocols taking two to three years to complete. Patients with standard and medium risk ALL are treated with chemotherapy programs which last two to three years. A common structure for ALL treatment is sequential phases of chemotherapy including: (i) induction and consolidation; (ii) interim maintenance (CNS protection); (iii) delayed intensification (re-induction and consolidation); and (iv) maintenance chemotherapy, which is a prolonged but less intensive phase. Patients found to have high risk ALL are treated more intensively and may include (i) induction and consolidation; (ii) up to 6 courses of intensive high-risk chemotherapy; (iii) delayed intensification (re-induction and consolidation); and (iv) maintenance chemotherapy. A small number of patients with high risk ALL (typically high risk ALL with poor MRD response) are recommended to receive (i) induction and consolidation; (ii) up to 3 courses of intensive high-risk chemotherapy followed by allogeneic haematopoietic stem cell transplantation.^{10, 38, 42, 43} The specific treatment regimens and selection of drugs, dose schedules, and treatment durations will differ between paediatric and adult patients. CNS prophylaxis and/or treatment will also be given at intervals throughout therapy. It should be noted that there are some specific genetic abnormalities (e.g. Ph-positive-ALL^c treated with tyrosine kinase inhibitors such as imatinib, nilotinib, dasatinib or ponatinib³⁷) that are critical to identify for disease evaluation, optimal risk stratification, and treatment planning.

^b HLA typing and bone marrow transplant referral should be considered for all newly diagnosed and relapsed transplant-naïve patients to facilitate timely donor identification, and ultimately allogeneic transplant if warranted.¹⁰ NCCN (2021)

^c Ph = Philadelphia chromosome

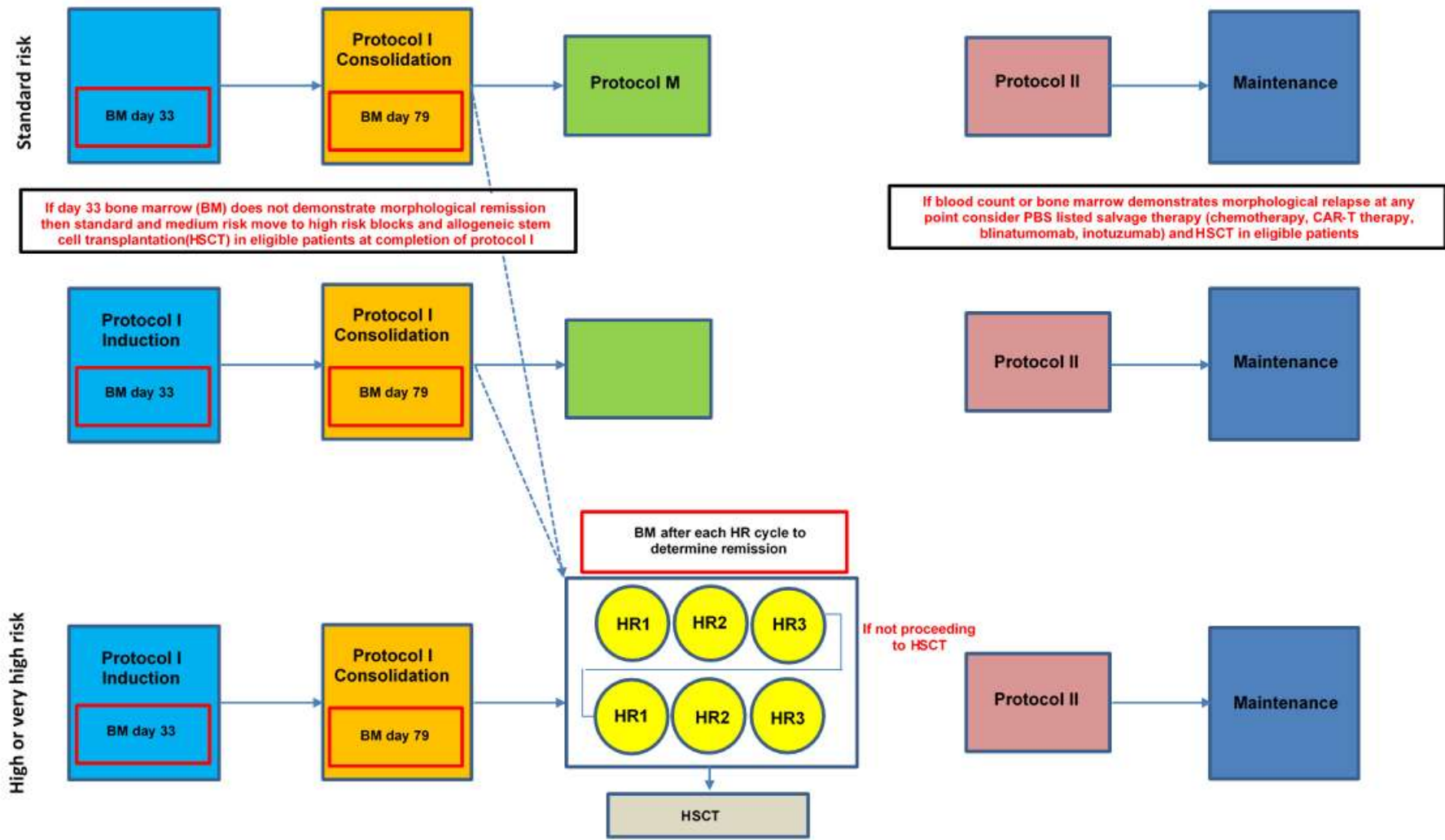


Figure 2 Current clinical algorithm for patients diagnosed with ALL. (below, derived from the EviQ guidelines www.evip.org.au)

PART 6b – INFORMATION ABOUT THE INTERVENTION

28. Describe the key components and clinical steps involved in delivering the proposed medical service:

Following diagnosis of acute lymphoblastic leukaemia, or relapse with this disease, a bone marrow aspirate is sent to the testing laboratory for the identification of leukaemia-specific molecular markers or a leukaemia-specific immunophenotype pattern (i.e. an aberrant combination of expression of surface antigens). Testing the diagnostic leukaemia sample for the presence of MRD markers is critical to avoid use of markers present only on subclones that potentially cause false negative results in later MRD tests or false positives if detecting rare combinations on normal lymphoblasts. At the point of presentation, in most patients >85% of lymphocytes are leukaemic blasts, enabling the leukaemia signature to be clearly defined.

Follow up bone marrow aspirate samples are collected after successive blocks of therapy defined by the protocol and sent for the measurement of one or two leukemic molecular markers or measurement of cells with the leukaemia-specific immunophenotype pattern. This stage requires inclusion of critical controls or comparisons to avoid false positive and false negative results. These tests are performed and interpreted according to established guidelines in an accredited laboratory subject to QAP.

To monitor MRD, both flow cytometry cell-based and molecular DNA-based methods are available. Each technique has advantages and disadvantages, and all require significant expertise so choice of technique can also depend on laboratory expertise or experience as well as the threshold of detection required. Methods for MRD detection need to be specific, highly sensitive, reproducible and broadly applicable.

Current molecular methods for MRD detection identify and quantitate clonal rearrangements found in ALL cells. Normal precursor B and T cells rearrange the immunoglobulin (IG) and/or T cell receptor (TR) loci during normal immunological development. Each B or T cell rearranges these genetic alleles in a unique manner allowing the identification of the malignant-associated clonal rearrangement of DNA at diagnosis to be measured over time with treatment. In this setting, eradication of the malignant clone is determined by amplification of the immunoglobulin or T cell receptor locus by a polymerase chain reaction with identification of the malignant clone either by direct sequencing (in next generation sequencing techniques) or by the derivation of primers specific for the malignant clone in allele-specific oligonucleotide quantitative PCR (ASO qPCR).⁴⁴ The specially designed ASO qPCR tests use two primers, one unique to the patient and a segment-specific fluorescent hydrolysis probe for additional sensitivity. Some patients, particularly those with immature ALLs have subclones with different Ig/TCR markers, so two markers are preferred and screening is performed to identify markers that can still be quantitatively measured when the sample is diluted 1 in 10,000 (10^{-4}).⁴⁵⁻⁴⁹ The use of qPCR MRD is well standardised for multi-site clinical trials through the EuroMRD group and is currently the method of choice for large international ALL trials in children and adults registered in Europe.

Multi-parametric flow cytometry (MPFC) is used to detect aberrant combinations of expression of lymphocyte cell surface proteins on individual cells. MPFC methods can be used in the majority of ALL patients (>95%) and provides information about the immunophenotypic heterogeneity of leukaemia and the cellular status of the bone marrow microenvironment that other MRD detection methods lack. MPFC is a relatively low-cost technique, with a fast turnaround time; however, it requires a large number of live cells (which may be technically difficult to obtain), as well as timely sample preparation and laboratory processing. MPFC identifies residual leukaemic cells based on surface protein expression (immunophenotyping), with samples incubated with fluorochromes conjugated to antibodies specific to proteins of interest. A patient specific or universal standardised approach can be used to identify leukaemic cells. The patient specific approach uses flow cytometry at diagnosis to generate specific antigen profiles or leukaemia-associated immunophenotypes (LAIPs). LAIPs can be used after induction to look for residual disease in a case specific manner; however, it is possible for LAIPs and normal cell populations to change over the course of treatment.^{45, 50-52} The universal approach identifies leukaemic cells by how they deviate from normal haematopoietic cell populations using a defined set of antigens; however, this technique requires a high-level understanding of antigen expression throughout different lineages and maturation states in order to distinguish cell types.⁵³

Molecular and flow cytometry methods for MRD detection are considered complementary as many individuals may be followed with both methodologies but specific ALL cases occur where only one of

these methods is able to identify a suitable ALL-associated marker to use over time. It is envisaged most patients would have MRD monitored by one or both of the listed methods.

29. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

N/A

30. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

N/A

31. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

No limitation should be placed on the number of services that each patient can receive. Whilst the majority of patients will require less than 4 tests throughout their treatment, those patients who respond poorly may need repeat MRD testing until they go into complete molecular remission. Patients who experience ALL disease relapse will also require additional testing as further attempts at cure may be undertaken. Patients who have had bone marrow transplantation, immunotherapy or CAR-T therapy may also require MRD monitoring. It should be noted; however, that the average number of MRD tests that a patient may need would not exceed 4 per year for three years (i.e. 12 in total). An additional 12 measurements may be reasonable in the relapsed disease setting.

32. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:

Nil

33. If applicable, advise which health professionals will primarily deliver the proposed service:

This service requires referral by an oncologist or haematologist and collection of patient samples under anaesthesia in hospital. The MRD diagnostic test will be delivered by trained scientists in an accredited laboratory. Testing would be requested by the treating clinician and provided by Approved Practising Pathologists in line with other tests on the MBS Pathology Table.

34. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

N/A

35. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

Patients should be referred by a specialist haematologist/oncologist or consultant physician.

36. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:

Testing would be delivered only by Approved Practising Pathologists in NATA Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral only by registered Medical Practitioners (non-pathologists – haematologists and oncologists) in line with other tests in the MBS Pathology Table.

37. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select ALL relevant settings):

- Inpatient private hospital (admitted patient)
- Inpatient public hospital (admitted patient)
- Private outpatient clinic
- Public outpatient clinic
- Emergency Department
- Private consulting rooms - GP
- Private consulting rooms – specialist

- Private consulting rooms – other health practitioner (nurse or allied health)
- Private day surgery clinic (admitted patient)
- Private day surgery clinic (non-admitted patient)
- Public day surgery clinic (admitted patient)
- Public day surgery clinic (non-admitted patient)
- Residential aged care facility
- Patient's home
- Laboratory
- Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

N/A

38. Is the proposed medical service intended to be entirely rendered in Australia?

- Yes
- No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

39. 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 (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

Morphological examination of a bone marrow aspirate would be the appropriate comparator. After obtaining the bone marrow sample, a slide is prepared, stained with Giemsa before its morphology is examined under a microscope (Figure 3). To better define the residual leukaemic burden, immunophenotyping needs to be performed.⁵⁴ Typically, morphology can detect down to approximately five lymphoblasts (ALL cells) in 100 white cells. This is very insensitive to residual leukaemia after treatment.

Cytogenetic analysis is also frequently performed on bone marrow aspirates. This genetic technology will allow leukaemia cell burden to be measured to approximately 5 in 100 cells if a clonal cytogenetic marker is identified.

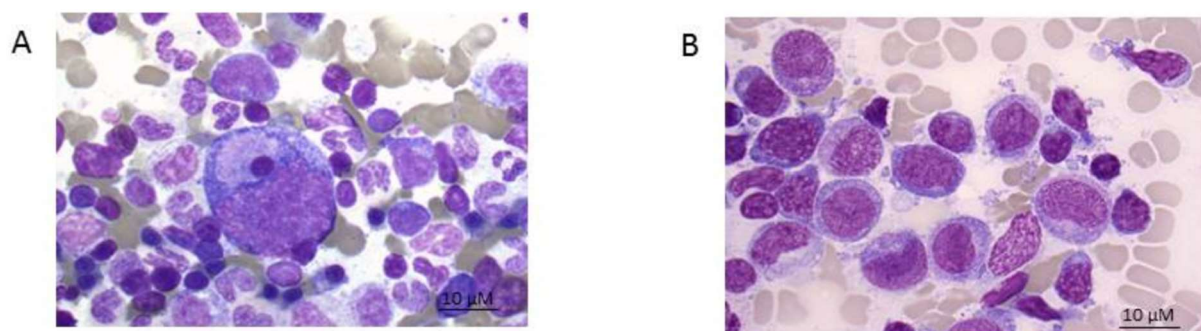


Figure 3 Bone marrow smear. A) shows the smears of healthy bone marrow consisting of different functional cell types and B) an AML patient with predominantly leukaemic blasts. Giemsa stain shown at 100x magnification.⁵⁴

40. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

- Yes (please list all relevant MBS item numbers below)
- No

MBS item number 65087

Bone marrow - examination of aspirated material (including clot sections where necessary), including (if performed): any test described in item 65060, 65066 or 65070

Fee: \$83.10 Benefit: 75% = \$62.35 85% = \$70.65

MBS item number 73290

The study of the whole of each chromosome by cytogenetic or other techniques, performed on blood or bone marrow, in the diagnosis and monitoring of haematological malignancy (including a service in items 73287 or 73289, if performed). - 1 or more tests.

Fee: \$394.55 Benefit: 75% = \$295.95 85% = \$335.40

MBS item numbers required to obtain the bone marrow aspirate

MBS item number 20440

INITIATION OF MANAGEMENT OF ANAESTHESIA for percutaneous bone marrow biopsy of the sternum (4 basic units)

Fee: \$82.40 Benefit: 75% = \$61.80 85% = \$70.05

MBS item number 21112

INITIATION OF MANAGEMENT OF ANAESTHESIA for percutaneous bone marrow biopsy of the anterior iliac crest (4 basic units)

Fee: \$82.40 Benefit: 75% = \$61.80 85% = \$70.05

MBS item number 21114

INITIATION OF MANAGEMENT OF ANAESTHESIA for percutaneous bone marrow biopsy of the posterior iliac crest (5 basic units)

Fee: \$103.00 Benefit: 75% = \$77.25 85% = \$87.55

MBS item number 21116

INITIATION OF MANAGEMENT OF ANAESTHESIA for percutaneous bone marrow harvesting from the pelvis (6 basic units)

Fee: \$123.60 Benefit: 75% = \$92.70 85% = \$105.10

- 41. Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):**

The comparator is morphological examination of a bone marrow aspirate. Therefore, the clinical management pathway follows that as described in Figure 2, with the conventional care pathway as described in Q26. Residual ALL is determined by morphology of the bone marrow aspirate with a sensitivity of approximately 5 in 100 cells.

- 42. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?**

- In addition to (i.e. it is an add-on service)
 Instead of (i.e. it is a replacement or alternative)

- (b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:**

MRD testing by flow or molecular methods represents clinical best practice with the National Comprehensive Cancer Network clinical practice guidelines recommending the quantification of MRD whenever possible for all patients with ALL.¹⁰ In Australia, MRD testing has been considered standard of care for children with ALL for more than 10 years. However, as MRD is not currently funded by the MBS, some adult patients may still undergo residual disease testing by morphology. If approved, it would be expected that MRD testing would completely replace residual disease testing by morphology within a very short period of time for adult patients. A bone marrow biopsy will still need to be performed, however, as MRD testing is typically performed on a bone marrow sample as this is currently a more

sensitive method for MRD analysis in ALL compared to peripheral blood testing. Morphology would still be performed on bone marrow aspirates as interpretation of the MRD test requires an understanding of the B- or T- cell infiltrate of the bone marrow compared to the other myeloid haematological elements.

43. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):

After treatment and during the maintenance phase, periodic MRD testing should be conducted (no more than every 3 months) for patients in complete remission (undetectable levels), with the frequency of MRD testing increased if detectable levels of disease are present. After induction and consolidation treatment and during the maintenance phase, periodic MRD testing should be conducted (no more than every 3 months) for patients in complete histological remission (<5% blasts), MRD testing should be performed before and after allogeneic haematopoietic stem cell transplantation.¹⁰

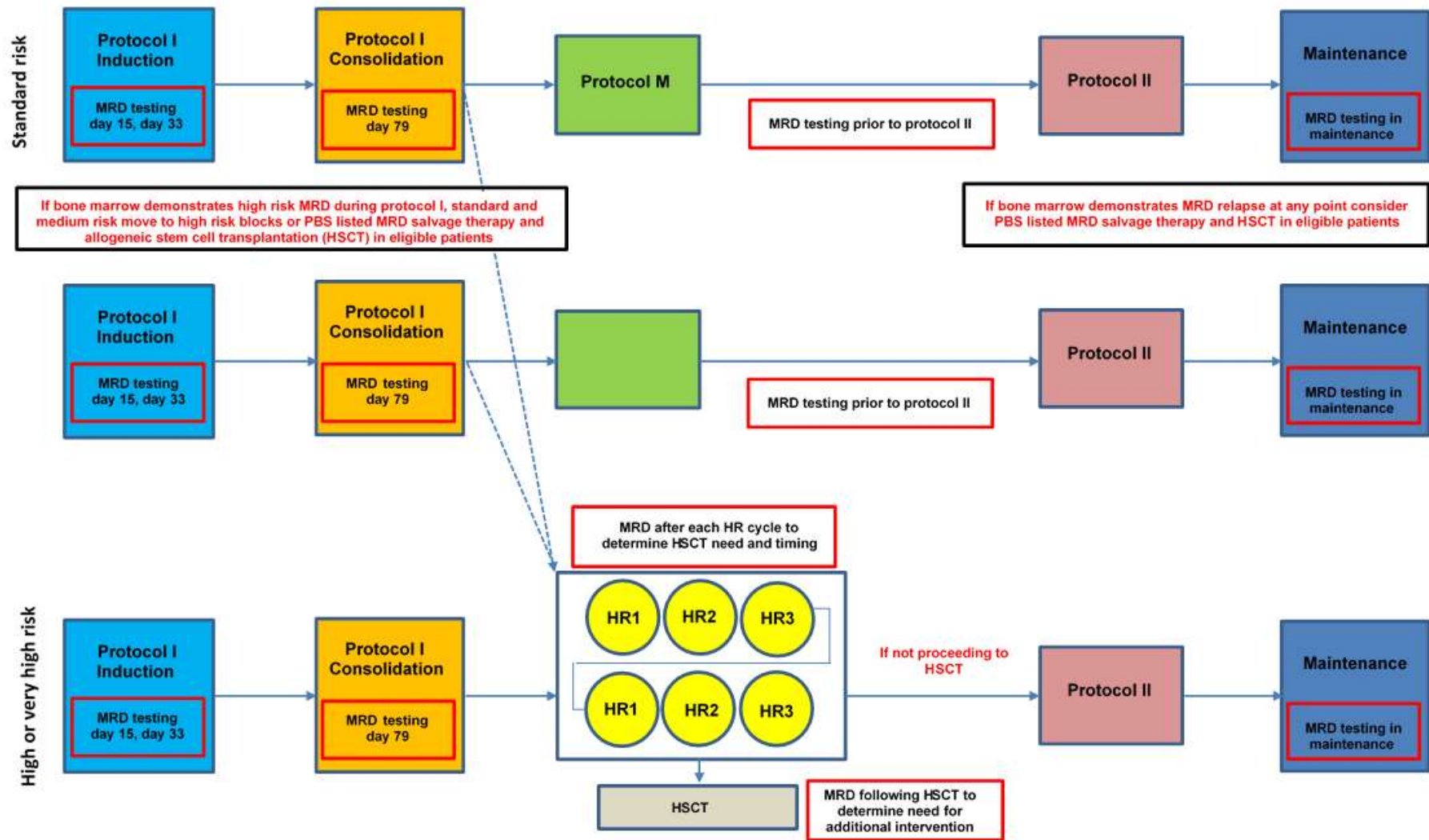


Figure 4 Clinical algorithm for the detection of MRD in patients diagnosed with ALL. (below, derived from the EviQ guidelines www.evip.org.au)

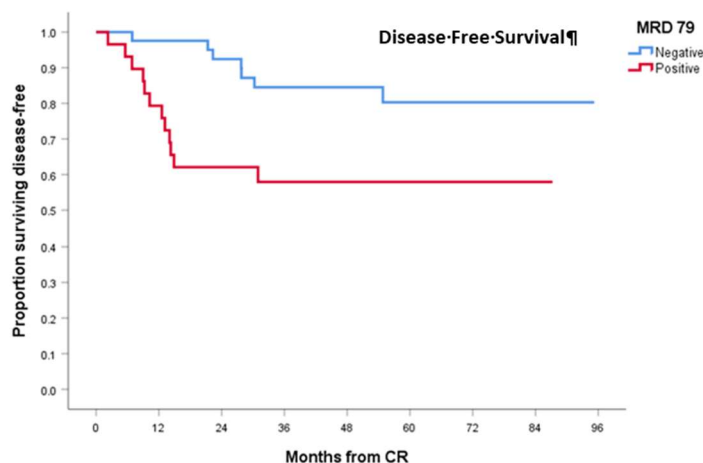
PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

44. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

Compared to BM morphologic assessment, multiple clinical trials have shown MRD assessment to be the single most important prognostic marker in assessing ALL response in both newly diagnosed and relapsed ALL patients.^{13, 14, 16, 25, 26, 28} As a result, MRD assessment has a central role in aiding clinicians to select appropriate risk and response adapted treatment for individual ALL patients. For newly diagnosed patients, MRD results guide treatment choices including risk group allocation, treatment intensity and identification of patients who would benefit from intensified therapy including intensive chemotherapy, immunotherapy and/or haematopoietic stem cell transplantation (HSCT – also known as bone marrow transplantation).^{13, 14, 25, 26} For patients with high risk ALL, relapsed ALL and those receiving immunotherapy or SCT, MRD monitoring during and after treatment identifies patients with a higher risk of treatment failure and relapse.^{16, 21, 28, 29}

Prior to the introduction of MRD assessment ALL risk group allocation and treatment selection was based predominantly on clinical and laboratory features present at diagnosis (age, white cell count, cytogenetics) with little opportunity to modify therapy based treatment response as most patients initially achieve morphological complete remission. In those that achieve complete remission, MRD response monitoring facilitates the identification of patients who can be treated with less intensive therapy (standard risk patients with no detectable MRD) as well as identifying patients most likely to benefit from intensified therapy (high risk patients with detectable MRD). Patients with an excellent MRD response can be treated with less intensive and less toxic therapy whilst more intensive and more toxic therapies are limited to those most likely to benefit from them.

Recently published Australian data from the ALL06 study reports on the 3-year follow-up MRD outcomes in 15–39-year-old (median 22.7 years) ALL patients (n= 82 at induction). All patients in this study underwent Induction therapy and treatment protocol 1 (TP1) before being stratified into treatment protocols based on their risk as determined by MRD status (standard, medium, high and very high-risk) (See [Appendix 1](#) for protocol). After TP2, patients who were MRD negative had an 80% lower risk of death compared to those who were MRD positive (95%CI [0.06, 0.64], p=0.007), and a 25% increase in survival time (Figure 5). Patients with good MRD response and no other risk factors received standard therapy and were spared HSCT/BMT. All other patients could then be considered for high-risk therapy and HSCT/BMT in their first morphological complete remission.³¹



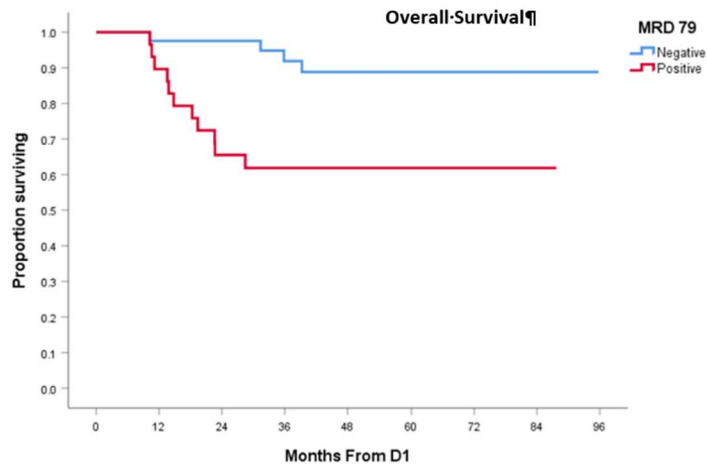


Figure 5 Impact of TP2 MRD on Disease-free survival and Overall Survival³¹

This study clearly demonstrates a survival advantage for those patients who achieved morphological remission who were MRD negative at day 79 versus those that remain MRD positive and who could be spared additional intensive therapy and HSCT/BMT in first complete morphological remission. Early identification of patients who would be considered at high risk of relapse by virtue of MRD result could proceed to additional intensive therapy and HSCT in morphological complete remission to improve long term outcomes.³¹

Another small Australian study described the clinical utility of MRD testing in 24 children with relapsed/refractory precursor B-cell acute lymphoblastic leukaemia (B-ALL) treated with blinatumomab. An MRD response of 58% was reported, demonstrating that not all children with B-ALL will respond to blinatumomab. Treatment with blinatumomab resulted in better outcomes in children who became MRD negative (Figure 6). The addition of MRD facilitates treatment decision-making, with MRD positive patients being unlikely to respond to additional treatment with blinatumomab. Based on MRD results, treatment with the expensive blinatumomab can cease and alternative treatment options can (successfully) be explored such as haematopoietic stem cell transplant or CD19-directed chimeric antigen receptor T-cell therapy.²⁷

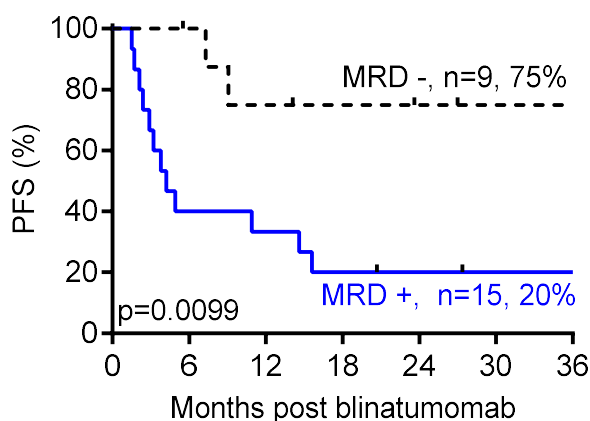


Figure 6 Kaplan Meier graph of Progression Free survival²⁷

45. Please advise if the overall clinical claim is for:

- Superiority
 Non-inferiority

46. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Safety Outcomes:

- Test adverse events
- Adverse events from subsequent treatment
- Adverse events from change in patient management

Clinical Effectiveness Outcomes:

- Change in management/treatment resulting in change in patient health outcomes: mortality, morbidity, quality of life

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

47. Estimate the prevalence and/or incidence of the proposed population:

In 2015, the incidence of ALL in Australia was 389 patients (combined adult and paediatric), with a relative survival rate of 74% (Table 2). It is expected that the number of ALL patients would increase by an estimated 3% per year. Although ALL can occur at any age, there are two distinct peaks of incidence: early age onset (<10 years of age) and late onset (\approx >65 years), as described in Figure 7.

Table 2 Incidence (2015), mortality (2016) and 5-year relative survival (2011–2015) of Acute lymphoblastic leukaemia⁴¹

Cancer type (ICD-10 code)	Incidence		Mortality		Relative survival (%)
	Number	ASR	Number	ASR	
Acute lymphoblastic leukaemia (C91.0)	389	1.6	97	0.4	74.0

ASR = age standardised rate

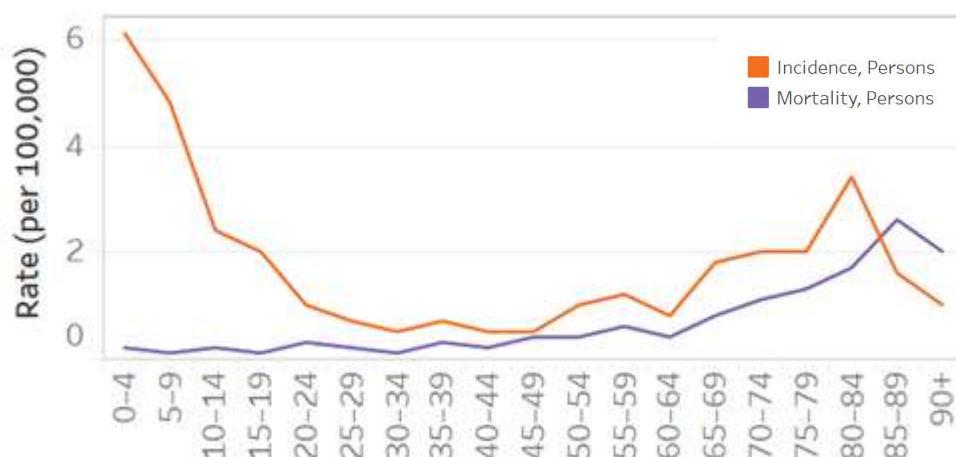


Figure 7 Estimated age-specific rates of acute lymphoblastic leukaemia in Australia, 2020³⁹

48. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

It would be expected that most paediatric ALL patients may require MRD testing an average of four times in the first year, and annually for three years post-diagnosis. Adults may require more testing as disease clearance is slower and often incomplete. Further testing would be required in those individuals who experience ALL relapse or long toxicity related delays, and high-risk patients receiving expensive targeted therapies or more intensive therapy including bone marrow transplant.

49. How many years would the proposed medical service(s) be required for the patient?

Three years, unless the patient relapses. ALL disease relapse should be treated like a new diagnosis as patients recommence multi-agent chemotherapy and their MRD response to re-instituted chemotherapy is monitored closely in the first year.

50. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

The number of patients expected to access the service in the first full year would be the number of adults and paediatric patients diagnosed with ALL (n= 445).

51. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of ‘leakage’ to populations not targeted by the service:

Data from the AIHW indicate that the incidence of all haematological malignancies combined has increased only marginally over time at an average rate of 3.1 per cent.^d It would be expected that this rate would remain constant over the next three years. Expected numbers of patients acute lymphoblastic leukaemia is summarised in Table 3.³⁹

It would be expected that ALL patients may require MRD testing an average of four times per year, for up to three years post-diagnosis.

Table 3 Expected number of new patients with acute lymphoblastic leukaemia haematological malignancy in Australia³⁹

	2020	Expected 2021	Expected 2022	Expected 2023
New ALL patients each year (a 3% increase per year)	445	458	472	486
Cumulative number of patients undergoing MRD testing in any one year	445	903 (445 + 458)	1,375 (445 + 458 + 472)	1,416 (458 + 472 + 486)

^d Average increase calculated from the increase of cases each year from 2017-2020. ³⁹ Australian Institute of Health and Welfare 2020

PART 8 – COST INFORMATION

52. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

MRD measured by Flow cytometry = \$550

Cell Processing and data capture \$160, Reagents including Fluorochrome-labelled antibodies \$110, Scientific Labour cost \$280

MRD measured by Molecular methods = \$1150

ASO-qPCR Costing: Initial patient-specific assay development costs \$2,220 which includes \$620 for reagents and sample processing and \$1,600 staff costs reflecting unique PCR assay development for each individual patient. The cost of MRD testing once the patient-specific assay is developed is \$780, which includes \$220 for reagents and sample processing and \$560 for staff costs.

NGS Costing:

Sample processing and DNA extraction \$100, Sequencing reagents \$900, Scientific labour costs \$150

53. Specify how long the proposed medical service typically takes to perform:

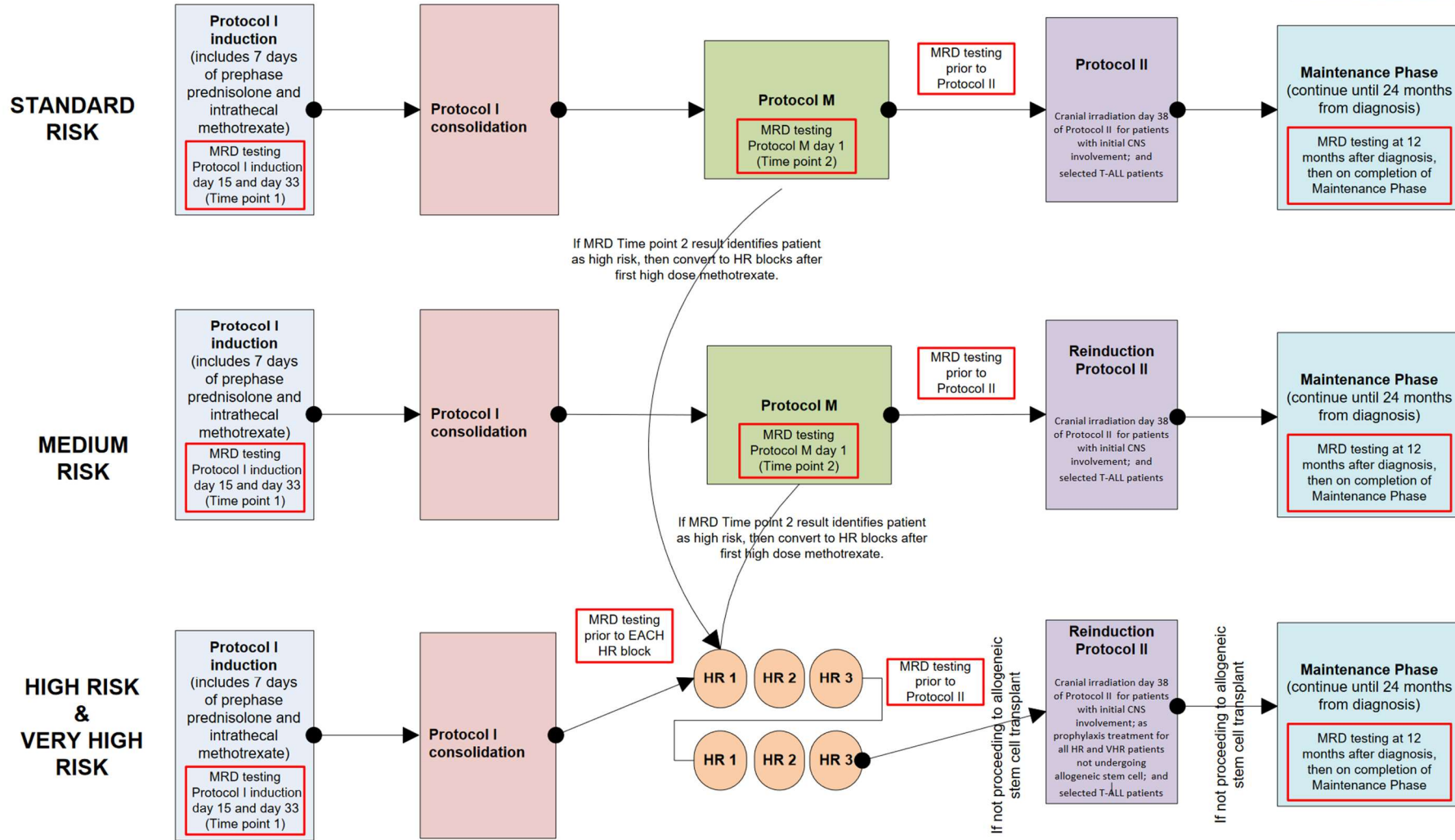
MRD testing using flow cytometry can be completed within 2 days after sampling. The turnaround time for MRD testing and reporting with qPCR is approximately 3-5 days, except in the case of a first test for ASO-qPCR where results take 3 weeks to allow for unique assay development.

54. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

Category 6 – Pathology services Group P1 Haematology, Group P6 Cytology
Minimal residual disease testing by flow cytometry in patients diagnosed with acute lymphoblastic leukaemia (ALL) treated with combination chemotherapy treatment or after salvage therapy. Maximum of 12 per episode of disease. Fee: \$550

Category 6 – Pathology services Group P1 Haematology, Group P6 Cytology
Minimal residual disease testing by a molecular methodology in patients diagnosed with acute lymphoblastic leukaemia (ALL) treated with combination chemotherapy or after salvage therapy. Maximum of 12 per episode of disease. Fee: \$1150

Appendix 1



<https://www.eviq.org.au/getmedia/44bb07dc-cf6f-4186-9919-43657ec1df2a/ID-3825-ALL06-Protocol-flow-diagram.pdf.aspx>

Appendix 2

Overview of new diagnosis ALL therapy before MRD						
		Standard Risk	Medium Risk	High Risk	Tests	
	Risk criteria	WCC<20 & Age 1-6y & No HR features	WCC>20 or Age<1 or >6 T-ALL	Poor prednisone response No remission end induction High risk genetics	Standard tests for all ALL patients	Standard tests only for HR ALL patients
Time point	Diagnosis				FBC BM CG	
Treatment	1 st week	Steroid pre-phase			FBC	
	Induction therapy	Common induction therapy			BM	
					BM	
	Consolidation therapy	Common consolidation therapy				
					BM	
	Interim maintenance (HD-MTX)	Common interim maintenance		HR-1		
				HR-2		BM
				HR-3		BM
				HR-4		BM
				HR-5		BM
				HR-6		
	Delayed intensification	Common delayed intensification			BM	
	Maintenance therapy	Common maintenance therapy				
	End of treatment				BM	

Overview of new diagnosis ALL therapy with MRD												
	Risk criteria	Standard Risk No HR features MRD ^{negative} after induction &/or consolidation	Medium Risk No HR features MRD ^{low positive} after induction	High Risk Poor prednisone response No remission end induction High risk genetics MRD ^{high} during, after induction & consolidation	Standard tests for all ALL patients	Additional MRD	Tests Standard tests only for HR ALL patients		Additional MRD for HR ALL patients			
							Chemo	SCT	HR patients	SCT patients		
Time point	Diagnosis				FBC, BM, CG							
Treatment	1 st week	Steroid pre-phase			FBC	MRD						
	Induction therapy	Common induction therapy			FBC, BM	MRD						
					FBC, BM	MRD						
					FBC, BM	MRD						
	Consolidation therapy	Common consolidation therapy										
					FBC, BM	MRD						
	Interim maintenance (HD-MTX)	Common interim maintenance		HR1								
				HR2				BM		MRD	MRD	
				HR3				BM		MRD	MRD	
				↙↘ MRD ^{low} MRD ^h								
				HR4	SCT				BM		MRD	
				HR5					BM		MRD	
	Delayed intensification	Common delayed intensification				FBC, BM		BM		MRD		
	Maintenance therapy	Common maintenance therapy						BM		MRD		
	End of treatment				FBC, BM							

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