RAPID ACCESS TO NEW DRUGS AND TREATMENTS FOR PEOPLE WITH BLOOD CANCER ON THE NHS

Blood Cancer Alliance

FOREWORD

On behalf of the whole membership of the Blood Cancer Alliance, I would like to thank you for taking the time to read this important new research report.

There are currently over 240,000 people in the UK living with blood cancer. It is the fifth most prevalent cancer in our country, and the third biggest cancer killer. Improving outcomes for blood cancer patients - both in terms of disease survival and quality of life – is the ambition that drives the Blood Cancer Alliance, with our member organisations working individually and collectively towards this goal every single day.

The Blood Cancer Alliance commissioned this research in order to strengthen the evidence base for how, by making positive policy changes with regard to new blood cancer treatments, the Government and their arm length agencies, the pharmaceutical industry, and the wider blood cancer community can secure better patient outcomes.

When it comes to treatment, blood cancers are more complex than solid tumour cancers. Surgery and radiotherapy are rarely an option. Ensuring blood cancer patients have timely access to the best and most effective new medicines and treatments is, therefore, critical to improving patient outcomes.

The research contained in this report identifies that patient access to new and effective treatment is still variable across the UK. We outline ten issues that are exacerbating this problem. The policy recommendations we are making are by no means radical. They represent changes that agencies such as the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), commissioners and the pharmaceutical industry can make to their practices that would improve access to blood cancer treatments. We expect that many would also aid access to treatments for all patients as it matters that patients are involved every step of the way; from development through to prescription in the NHS. They also include steps the Department of Health and Social Care (DHSC) could take to promote patient confidence that new medicines will be accessible. Examples of what we are advocating for include; involvement of patients in the treatment appraisal process that makes a tangible difference, better use of real-world data and evidence, enhanced preparedness for appraising the strong pipeline of new treatments and more progress on flexible pricing.

The future of blood cancer treatment is promising, with many new treatment options on the horizon. However, this means little if they cannot be accessed by the patients that need them. As the Cancer Drugs Fund (CDF) changes to the Innovative Medicines Fund, securing the continuation of this level of available investment in blood cancer treatment will be important in making sure that blood cancer patients' treatment needs can be better met in the future.

We are very clear that within the complexities of new treatment development, appraisal, pricing and funding, the patient voice is currently lost. If implemented, the recommendations made in this report would not only help improve outcomes in blood cancer but would also put the patient interest and voice firmly back in the centre of the process.

Zack Pemberton-Whitely
Chair,
Blood Cancer Alliance

Blood Cancer Alliance

ACKNOWLEDGEMENTS

This report is the result of a collaboration between patients who shared their views in an online survey, members of the Blood Cancer Alliance, experts who shared their views in telephone interviews, Leela Barham, an independent researcher and Atlas Partners. Everyone who participated generously shared their time and expertise. The Blood Cancer Alliance would like to thank everyone for their input. That said, this report reflects the view of the Blood Cancer Alliance alone.

Whilst the Blood Cancer Alliance receives funding from the pharmaceutical industry for the work it carries out, it is wholly independent of these commercial organisations, including in its decision making, and has rigorous governance structures to ensure that independence. For more information please contact info@bloodcanceralliance.org

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EXECUTIVE SUMMARY

The Blood Cancer Alliance is a coalition of charities that represent people living with blood cancer. The Alliance commissioned the research that underpins this report to explore the current opportunities and challenges for rapid access to new drugs and treatments for people with blood cancer in all four nations of the UK, and to identify recommendations for change.

The research included a rapid evidence review, an environmental scan, one-to-one anonymised telephone interviews with seven experts during May and June 2020 and an online survey of patients and/or carers of those with blood cancer that was run from 17 June to 1 July 2020. Over 700 patients and carers responded. The Alliance wanted to take an evidence-based approach as well as learn from the real experiences of patient organisations who have participated in appraisals.

Treatment for blood cancer is complex including combinations of treatments for some patients. Treatment options are expanding with close to a third of new cancer treatments launched between 2014-2018 for leukaemia, lymphoma and multiple myeloma. Some of these new treatments, such as CAR-T cell therapy, have the potential to be a cure for some blood cancers; they are not, however, going to be a panacea and the Alliance believes that there will remain unmet patient needs given the vast range of blood cancer types.

Getting access to treatments for blood cancer is variable in the UK. Patients who responded to the online survey have highlighted that it can be difficult to access targeted therapies and other treatments. It can be frustrating for patients when treatments are available in some parts of the UK, but not all. That said, there are patients who report a great experience with the NHS and with accessing treatments. The Alliance wants to see all patients have positive experiences of care and access to the treatments that are clinically appropriate for them.

The ease of access – in the sense of approved by a regulator and NHS funded - to blood cancer treatments is the result of a number of factors. They include recommendations made by the UK's Health Technology Assessment (HTA) agencies including the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC). Some patients are aware of these agencies and know that their recommendations may mean that they cannot access blood cancer treatments on the NHS. Some treatments are available through specific funding mechanisms, such as the Cancer Drugs Fund (CDF) in England. The ways that HTA agencies make decisions are controversial. These agencies have been changing in recent years; offering more opportunities for companies to engage early to discuss evidence that they need for NICE, for example. Further change may result from an ongoing internal review of methods used by NICE. How HTA is conducted will influence future access to blood cancer treatments: NICE has 70 ongoing appraisals in blood cancer. Many of these present challenges because they are used in combination or are treatments for many indications. The agency is generally facing a higher workload despite a rising trend of non-submissions, exacerbated by the COVID-19 global pandemic and their provision of clinical guidance to support management of patients against this challenging background.

Access to blood cancer treatments is also related to the commercial negotiations conducted by NHS England (NHSE), the biggest buyer for specialised medicines in the UK and individual companies. NHSE has a draft commercial framework which will shape future agreements made with companies. NHSE and most companies work within the framework for pricing of medicines that is set out in the Voluntary Scheme for Branded Medicines Pricing and Access (VS). Finally, the price of treatments also plays a very significant role in access too.

The research has found that there are ten major issues that need to be addressed to ensure rapid access to blood cancer treatments in the future. It is also clear that these are issues that need to be addressed through collaboration between all stakeholders, including industry and the government and their arms-length agencies.

Issue 1: New blood cancer treatments are coming through and HTA agencies and companies need to prepare for their appraisal.

Recommendation 1: The Alliance calls on the Association of the British Pharmaceutical Industry (ABPI) and the Department of Health and Social Care (DHSC) to provide a public statement on progress with the commitments on horizon-scanning made in the Voluntary Scheme. The ABPI and the DHSC should assess whether current efforts are sufficient or if more work is needed and provide a public statement.

Recommendation 2: The Alliance calls on NICE and the pharmaceutical industry to develop an evidence base on the benefits of early engagement, including when patients and their representative organisations are part of the dialogue. This should include, at a minimum, publishing within final Technology Appraisal (TA) guidance whether the company has sought advice (and from which service) to bring NICE into line with the transparency provided by the European Medicines Agency (EMA). This evidence base should encourage more companies to engage, support NICE to provide a quality service, and encourage and support patients and their representatives in participating in engagement activities in the future. The SMC should consider formalising the opportunity for early engagement within their processes too.

Issue 2: It is vital to involve patients from R&D and beyond and for their involvement to have an impact.

Recommendation 3: NICE should set out a programme to explore how to use quantitative patient preferences as part of NICE decision-making. The Alliance calls for further research to explore how quantitative patient preferences could be incorporated into economic modelling. The research should be published to enable other HTA agencies and stakeholders to learn from it.

Recommendation 4: The Alliance calls on industry, in collaboration with patients and their representative organisations, to develop an evidence base on the benefits of early engagement with patients and their representative organisations in industry R&D. This should include independent researchers. This evidence base should encourage more companies to engage patients and their representative organisations in R&D and encourage and support patients and their representatives in participating in engagement activities in the future. The research should be published to enable companies to learn from it and accelerate the involvement of patients.

Recommendation 5: NICE and SMC should develop an evidence base on their approaches to involving patients and their representatives with a focus on the difference it makes to decisions. At NICE this should

include the involvement of patients and their representative organisations as part of the technical engagement step in addition to the other ways the patient perspective is brought into appraisals. Generation of this evidence base should include not only patients and their representative organisations, but also bring in external independent researchers. This evidence base should encourage more patients and patient organisations to engage and encourage and support patients and their representatives in participating in HTA activities in the future. The research should be published to enable other HTA agencies to learn from it and to enable patient groups to learn how best to engage.

Issue 3: Modifiers – additional factors that are not easily incorporated into approach to the clinical and economic evidence used in HTA - play a role in HTA but need revisiting. NICE historically has had one modifier: flexibility for end of life treatments allowing NICE to recommend treatments that come at a higher cost per Quality Adjusted Life Year. At the SMC, a wider range of modifiers can be considered, including a treatment being a designated orphan treatment and possible bridging to another definitive therapy (e.g. bone marrow transplant). NICE must acknowledge the legitimate challenges in developing the evidence base for rare blood cancer treatments at the time of launch.

Recommendation 6: The Alliance calls on NICE to bring in a wider range of modifiers into their deliberations. We do not specify them here as NICE's ongoing work is looking into modifiers. We do however note the ongoing work of Cancer52 who have called for more modifiers, including rarity, to be used by NICE.

Recommendation 7: NICE should clarify the criteria (e.g. the size of the patient population that is considered small enough to qualify for the HST programme) as part of their review. Flexibility is needed too with respect to which treatments can go through the HST programme to ensure treatments for rare blood cancers are not disadvantaged by the Single Technology Appraisal (STA) process which takes a narrower perspective than the HST programme and does not allow for higher cost per QALYs.

Issue 4: The CDF has enabled access for blood cancer patients but a change to an Innovative Medicines Fund is causing concern for future access.

Recommendation 8: The Alliance is seeking reassurance from the Department of Health and Social Care that funding for the Innovative Medicines Fund will be sufficient so as not to disadvantage blood cancer patients – and other cancer patients – from accessing treatments that would otherwise have been available through the CDF before the move to an Innovative Medicines Fund.

Issue 5: Uncertainties are a common feature in the evidence base for blood cancer treatments at the time of appraisal and real-world evidence could help.

Recommendation 9: The Alliance calls on companies to proactively look for real-world evidence that could be used in their submissions to HTA agencies. Companies should provide a statement in their submission that they have done so.

Recommendation 10: The Alliance calls on HTA agencies to set out more detailed guidance to aid companies in considering what real-world evidence, including features of registries and patient group surveys, will be acceptable to support submissions. This should go beyond the submission if appropriate, to help guide real world evidence generation that can be conducted to address uncertainties at the time of appraisal. This will help send signals to all those involved in setting up and reforming existing real-world data sources about the needs of HTA agencies.

Issue 6: The CDF has enabled access for blood cancer patients and enables the generation of further evidence when there are uncertainties at the time of first appraisal, where a treatment is considered to have plausible potential to be cost-effective. However, within the CDF the evidence that NICE needs to counter uncertainty at the time of the first NICE appraisal is not always being collected. This could lead to the same challenge of lack of evidence at re-appraisal.

Recommendation 11: The Alliance calls on NICE and NHSE to ensure that there is a clear link between the main clinical uncertainties identified at the time of the first appraisal by NICE and the clinical data that is generated during the time that a treatment is within the CDF. Agreements reached with companies should ensure that the main clinical uncertainties are addressed in the evidence generation that they are responsible for, if appropriate. The DHSC, as sponsor of both NICE and NHSE, should raise this as part of its work to hold both agencies to account and this should be demonstrated in published meeting minutes.

Recommendation 12: Guidance on plausible potential to be cost-effective should be published by NHS England. This will aid company planning and help patient groups by informing their input into discussions on potential treatments to go into the CDF.

Issue 7: Non-submissions are rising in blood cancer. Key drivers include the challenge of combination pricing and the lack of multi-indication pricing; these issues may still apply even when there is a submission by influencing the price at which a company is willing to supply the treatment to the NHS.

Recommendation 13: The Alliance calls for the ABPI to update on progress on combination pricing and publish a road map to adopt a solution.

Recommendation 14: The Alliance calls on all stakeholders to address the issue of multi-indication pricing. It is no longer sufficient to offer some flexibilities in exceptional circumstances; treatments with multiple indications are now common place. Where agreements have permitted multi-indication pricing these should be assessed on what can be learnt to permit wider rollout so as to provide patient access.

Recommendation 15: When it comes to treatments that are not cost-effective at zero price, for example, because of the high cost of backbone therapy a solution needs to be found to ensure that patients can access the treatment and that there is a reasonable apportionment of reward to the value being generated to those companies whose treatments are being used. NICE could explore the discount required in backbone therapies, for example. This would provide signals to the company and the NHS as to the pricing changes that are needed.

Issue 8: There is more potential for outcome-based payment where companies are rewarded on the basis of the outcomes that their treatments generate. Current positions in the Voluntary Scheme and in the draft NHS England Commercial Framework are too vague and do not send a strong signal about the openness of the system to this approach.

Recommendation 16: DHSC and NHSE should state their current positions on outcome-based payment now that we are half way through the Voluntary Scheme lifetime.

Recommendation 17: All stakeholders should be actively monitoring the debate on outcome-based pricing and should pay attention to the results of the ongoing OHE research on outcome-based pricing in due course. DHSC and NHSE should formally respond to the results of the pilot.

Issue 9: Submissions to NICE have errors; submissions need to improve.

Recommendation 18: Companies and those that support them in producing models and submissions to NICE should consider using the NICE PRIMA service to help identify technical errors and improve validation processes. In all cases, companies and those that support them need to improve their processes to minimise errors and avoid causing delays.

Issue 10: Rapid access requires speedy collaboration.

Recommendation 19: Stakeholders have shown how they can work together to enable fast access, including through the COVID-19 pandemic, and this spirit of working together must continue and be turned into business as usual.

1. INTRODUCTION AND OBJECTIVES

Together, blood cancers are the fifth most common type of adult cancer, the most common cancer amongst children and the third most fatal cancer. Together, they claim more lives every year than breast or prostate cancer, however they remain widely unknown. Those living with one of these cancers face unique challenges whilst undergoing diagnosis, treatment and on-going care.

The Blood Cancer Alliance is a group of fourteen UK charities. Together, we are working to tackle the issues blood cancer patients face and improve the experience and outcomes of all those living with blood cancer. Unlike solid tumour cancers, blood cancers are often not treatable using surgery or radiotherapy and many are relapsing and remitting and require multiple episodes of treatment. Access to the most effective new treatments is therefore especially vital for blood cancer patients.

The Alliance commissioned the research that underpins this report to explore the current opportunities and challenges for rapid access to new drugs and treatments for people with blood cancer in all four nations of the UK, and to identify recommendations for change.

The remainder of this report sets out:

- The approach used to develop this report;
- The UK access landscape for blood cancer treatments;
- Our evidence-based recommendations.

Appendices provide more detail for the approach taken.

Blood Cancer Alliance

2. APPROACH

The Alliance set out a multi-methods approach to explore the challenges and opportunities for reform to improve access to blood cancer treatments in the UK. These included (in the order that they were conducted):

- **A rapid evidence review.** Rapid reviews are recognised as providing a useful approach to provide actionable and relevant evidence that is timely and cost-effective. They do not, however, follow all the steps in a systematic review.[i] The rapid evidence review did not include a formal assessment of quality and relied on a single researcher based on searches in Pubmed (see Appendix 1);
- **An environmental scan.** As defined in Charlton, Doucet, Azar et al (2019)[ii], an environmental scan is the "process of seeking, gathering and interpreting and using information from the internal and external environment of an organisation to inform strategic decision-making and to direct future organisations action";
- **One-to-one anonymised telephone interviews with seven experts**[1] during May and June 2020 to bring in contemporary viewpoints. Given the number of people who were able to participate, the issues that they have raised can largely be seen as anecdotal on their own, but they have resonance with the wider literature; and
- **An online survey of patients and/or carers of those with blood cancer** that was run from 17 June to 1 July 2020 to bring in contemporary viewpoints.[2]

Both the rapid evidence review and environmental scan looked at the last three years. This was to reflect the current situation and to keep the scope manageable within the available resources.

The methods built upon each other; for example, the rapid evidence review and environmental scan were used to inform both the structured discussion guide for use in one-to-one telephone interviews and also to identify experts and inform questions to pose to patients, as well as providing source material for later analysis.

In addition, ad hoc searches were conducted to identify contemporary discussion on themes that apply more generally and not just to blood cancer (e.g. on the value of hope).

Finally, based upon the knowledge of the Alliance, additional material was drawn upon to ensure that the landscape for accessing blood cancer treatments is adequately described (e.g. the rapid evidence review and environmental scan did not identify papers relating to funds in Scotland and Wales). This is important to ensure appropriate context is set out.

Thematic analysis has been used. Thematic analysis is a method for identifying, analysing, organising and describing and reporting themes within a data set.[iii] A highly pragmatic approach has been taken without a formal database of studies, reflecting limited resources. It should also be noted that the research has been conducted by a single researcher raising issues of the potential for unconscious bias. The research conducted to support the Alliance in developing this report should not be seen as comprehensive and others may have drawn different conclusions if they conducted the research.

A descriptive quantitative analysis has also been undertaken to identify trends in NICE recommendations for blood cancer treatments as well as for the closed questions in the online patient survey.

Final recommendations were developed during two co-creation virtual workshops with BCA members. The Alliance wanted to take an evidence-based approach as well as learn from the real experiences of patient organisations who have participated in appraisals.

[1] Requests for anonymous interviews were sent out during the COVID-19 pandemic. This is likely to have shaped the ability – not necessarily the willingness – of experts to take part. Calls were conducted with: a HTA lead in Scotland, a payer in England, an academic who is also a member of a NICE Technology Appraisal Committee, a member of staff at a centre of excellence for cell and gene therapy, a member of staff at an organisation representing the pharmaceutical industry and two members of staff at patient organisations.

[2] 737 people completed the survey (i.e. clicked through to the end). 80.7% were patients, 17.1% a family/informal carer and 2.2% neither of these (and subsequently filtered out). 82.2% lived in England, 2.6% in Northern Ireland, 8.3% in Scotland, and 5.6% in Wales and 1.4% outside of the UK (and subsequently filtered out). 1.5% were aged 0-18 years old, 1.5% 19-24, 58% 25-64, and 39% 65 and above.

Blood Cancer Alliance

3. THE UK ACCESS LANDSCAPE FOR BLOOD CANCER TREATMENTS

3.1 About blood cancer

There are over 100 types of blood cancer, including diseases such as leukaemia, lymphoma and myeloma, as well as much rarer kinds. This report also recognises a range of haematological malignancies, such as myelodysplastic syndromes (MDS), as blood cancers.

Blood cancer is the fifth most prevalent cancer in the UK, with over 240,000 patients currently living with the disease. It is the UK's third most fatal cancer, claiming more than 15,000 lives each year - more than breast or prostate cancer.

3.2 Treatment for blood cancer is complex

Unlike treatment of solid tumour cancers, blood cancers are often not treatable using surgery or radiotherapy. Blood cancer patients are therefore reliant on chemotherapies, targeted therapies, and in some cases, stem cell transplantation, for curative treatment or disease management.

Not everyone diagnosed with a blood cancer will receive immediate treatment, with some never receiving treatment at all. For example, though the majority of chronic lymphocytic leukaemia (CLL) patients will require treatment at some point, a minority will never be treated because the damaging and permanent side effects of treatment may outweigh the benefit offered. Though there is a growing range of treatments (that reflect the need to take into account the genetic profile, patient's fitness and their co-morbidities), access to newer treatments and accurate treatment analysis leading to specific patients getting the 'right' treatment is varied and still largely not available for first line treatment.

Diversity of treatment is echoed in the results of the online survey. This was not designed to be representative of the incidence and prevalence of blood cancers, as it was open to any and all respondents without any deliberate sampling strategy - and is related to the cancers that respondents had been diagnosed with (or the person they care for) (see Figure 1 and Figure 2).

Figure 1: What type of cancer have you/the person you care for been diagnosed with?

Answer choice		Response percent	Response total
1	Acute myeloid leukaemia (AML)	7.4%	53
2	Acute lymphoblastic leukaemia (ALL)	2.4%	17
3	Chronic lymphocytic leukaemia (CLL)	11.1%	79
4	Chronic myeloid leukaemia (CML)	7.0%	50
5	Hodgkin lymphoma	0.7%	5
6	Non-Hodgkin lymphoma (NHL)	7.3%	52
7	Myeloma	28.2%	201
8	Myelodysplasia (MDS)	26.3%	187
9	Myeloproliferative neoplasms (MPN)	3.4%	24
10	Don't know	0.0%	0
		Answered	712

Figure 2: What treatment was recommended by your doctor/the doctor for the person you care for?

Answer choice		Response percent	Response total
1	Watch and wait	32.1%	225
2	Chemotherapy	52.8%	371
3	Stem cell transplant	37.5%	263
4	Immunotherapy, an exaple is CAR-T therapy	4.1%	29
5	Targeted therapies, exapmles include monocolonal antibodies (MABs) such as Mabthera (rituximab), cancer growth blockers (inhibitors) such as Imbruvica (ibrutinib), Velcade (bortezomib), TKIs (thyrosine kinase inhibitors) such as Glivac (imatinib), Sprycel (dasatinib), Tasigna (nilotinib), Bosulif (bosutinib), Iclusig (ponatinib)	27.4%	192
6	Radiotherapy	10.4%	73
7	Surgery	2.6%	18
8	A treatment that was part of a clinical trial	10.1%	71
9	Not applicable	3.1%	22
10	Don't know	1.1%	8
		Answered	702

Note: Respondents could select more than one option.

3.3 New treatments have been launched in blood cancer

IQVIA research found that between 2014-2018, 57 oncology drugs were launched and of those, 31 per cent were for leukaemia, lymphoma and multiple myeloma.[iv]

Blood cancer has also seen brand-new treatment options. In June 2018, the European Medicines Agency (EMA) approved the first CAR T-cell therapies. These included Yescarta (axicabtagene ciloleucel) as an option for people with diffuse large B-cell lymphoma (DLBCL) or primary mediastinal large B cell lymphoma (PMBL) as well as Kymriah (tisagenlecleucel) for people with DLBCL. These treatments are licensed for use where patients have already had two courses of treatment but who need more. CAR T-cell therapy is complex and uses the patients' own immune system to destroy lymphoma cells.[v]

There is a great deal of enthusiasm about the future potential of CAR-T cell therapy.[vi] It is being talked about as the future fifth pillar of cancer treatment, alongside surgery, chemotherapy, radiation and targeted therapy. CAR-T cell therapy has the potential to be a cure. This raises questions about the appropriate discount rate to be applied in modelling used to inform NICE appraisals. Previous NICE guidance has allowed for a change to the practice of a common discount rate (3.5% for both costs and health benefit) to adopt a lower discount rate for health benefits of 1.5% in the case of treatment effects being sustained for a very long period, normally at least 30 years.[vii] The 1.5% has been used in an appraisal for a blood cancer treatment in practice, although this was criticised as it did not reflect the 3.5% in the current NICE methods guidance.[viii]

There is also hope for new tumour 'agnostic' cancer treatments, including their potential in blood cancers. NHS England has already indicated that it will seek to fast-track these new drugs.[ix]

There are also new treatments that have been recognised by the UK regulator, the Medicines and Healthcare Products Regulatory Agency (MHRA) as promising through the designation of the Early Access to Medicines Scheme positive (EAMS) scientific opinion.[x]

3.4 Access to treatments is variable

The survey of patients and carers asked about their experience of the ease of getting the right treatment(s) for their condition. The majority found it very easy or easy (68.6% of 656 respondents) but there are those who found it difficult or very difficult (8.4% of 656 respondents). Those who found it difficult or very difficult were most likely to be referring to 'other' treatments and targeted therapies (see Figure 3).

As an alliance representing patients, we need to avoid situations as described by a respondent:

"There was a time when I couldn't have the treatment I needed but it was available in Scotland which is 6 miles from where I live in England."

Survey Respondent

The Alliance wants to see more comments like:

"I have never tried to access any other treatment. My prescribed medication has always been readily available to me & worked well!"

Survey Respondent

"My care was outstanding. I have no concerns that had I needed any other care outside of my area that I would have got it."

Survey Respondent

Figure 3: You said it was 'Difficult' or 'Very difficult' getting the right treatment(s) for your condition/the condition of the person you care for. Did this apply to any treatment(s) in particular?

Answer choice		Response percent	Response total
1	Chemotherapy	17.6%	9
2	Stem cell transplant	13.7%	7
3	Immunotherapy, an exaple is CAR-T therapy	5.9%	3
4	Targeted therapies, exapmles include monocolonal antibodies (MABs) such as Mabthera (rituximab), cancer growth blockers (inhibitors) such as Imbruvica (ibrutinib), Velcade (bortezomib), TKIs (thyrosine kinase inhibitors) such as Glivac (imatinib), Sprycel (dasatinib), Tasigna (nilotinib), Bosulif (bosutinib), Iclusig (ponatinib)	25.5%	13
5	Radiotherapy	0%	0
6	Surgery	2%	1
7	Not applicable	41.2%	21
8	Don't know	3.9%	2
		Answered	51

3.5 HTA agencies in the UK provide recommendations to the NHS on treatments

In the UK, decisions about which treatments to make available on the NHS are made by various agencies. For example, the health technology assessment (HTA) body, the National Institute for Health and Care Excellence (NICE), makes recommendations on the clinical and cost-effectiveness (or value-for-money) of treatments through their Technology Appraisal (TA) programme.[xi]

NICE aims to make their recommendations as close as possible to launch in the UK, after regulators like the EMA have deemed a drug to be safe, high quality and efficacious.[xii] NICE recommendations draw on a range of evidence, primarily a submission from the company, but also evidence from other stakeholders, including patients and their representative organisations.[xiii] Research has highlighted that processes may undermine evidence collected from patient representatives, albeit this reflected processes in place before 2017.[xiv]

There are similar agencies who undertake the HTA role in the devolved nations, including the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG).[xv] Recommendations made by NICE typically apply to Northern Ireland,[xvi] and will also usually supersede AWMSG recommendations in Wales too.[xvii]

Recommendations made by the UK's HTA agencies are not always the same for blood cancer treatments. For example, the SMC did not initially approve CAR-T therapy Yescarta (axicabtagene ciloleucel) for adults in Scotland who relapse after treatment for diffuse large B-cell lymphoma (DLBCL). NICE did recommend Yescarta for use within the Cancer Drugs Fund (CDF)[xviii] (the CDF is discussed further below).

3.6 HTA recommendations are important for access to treatments

The recommendations made by HTA agencies are important because they can either recommend use or not, or sometimes recommend use for a smaller group of patients than in the marketing authorisation (NICE refers to this as optimised).[xix]

NICE TA recommendations are backed up by a legal requirement for the NHS to fund within 90 days.[xx] The funding requirement may be varied, at the request of NHSE, under the Budget Impact Test (BIT). The BIT was introduced in 2017 and includes an assessment of the financial impact of a technology during the first three years of use. Where the budget impact exceeds £20million, in any of the first three years, NHSE and the company will engage in commercial discussions.[xxi] Whilst clinicians can prescribe a treatment before an HTA agency makes its recommendation, there can be a reticence to do so.[xxii] In Wales there is a New Treatment Fund that provides access to treatments recommended by NICE and AWMSG within 60 days.[xxiii]

Yet it must also be recognised that NICE can and has been faster than its counterparts in other countries. For example, in the case of ixazomab (brand name Ninlaro) for patients with relapsed or refractory multiple myeloma, ixazomab was according to analysis by Armoiry, Spath, Clarke et al (2019) 'fairly rapidly recommended' for use in comparison to protracted pricing negotiations in France. [xxiv] The NICE recommendation reflected repositioning of the treatment (as 3rd or 4th line treatment), as well as new price discounts offered during the appraisal, and recommended use as part of the CDF (discussed below).

Respondents to the survey were aware of HTA agencies and their recommendations; 12.7% (7 people) of those who found it difficult or very difficult to access the right treatment for their condition (or the person they care for) cited the treatment not being recommended by NICE/SMC/AWMSG.

Recommendations can be different between the HTA agencies in the UK. Nine out of ten survey respondents disagreed or strongly disagreed that they couldn't access a treatment available somewhere else in the UK. In contrast, eight out of ten disagreed or strongly disagreed that they couldn't access a treatment that is available in countries outside the UK (see Figure 4).

The impact of a lack of access at the individual patient level can be devastating, as illustrated by a respondent to the survey who said:

"It is frustrating and heart breaking not to be able to access certain treatments, when your disease is progressing, due to current NICE guidelines even though they have been shown to have good results. This really does not make sense when you have responded well to a certain treatment in the past and you are not eligible to try it again at this stage due to NICE guidelines, yet nothing is working currently."

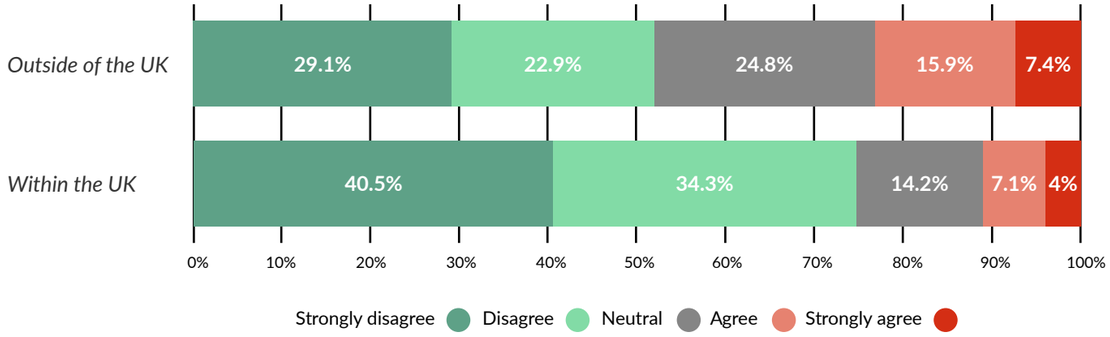
Survey Respondent

For other patients it is a matter of having private funding, an area which has little evidence to understand the scale that patients have to resort to in the absence of NHS access. A survey respondent said for their condition:

"I have never tried to access any other treatment. My prescribed medication has always been readily available to me & worked well!"

Survey Respondent

Figure 4: Please indicate how far you agree or disagree with the following statement: "I cannot/could not access a treatment that is available in countries outside of the UK" and "I cannot/could not access a treatment that is available in another part of the UK"



Base: 258 and 353 respectively. Note: In the context of these statements, agree and strongly agree are negative and hence they are coloured in shades of red.

3.7 The Cancer Drugs Fund in England can provide access to treatments

In England, NICE can recommend that a cancer drug is funded on an interim basis in the CDF.[xxv] The CDF, from July 2016, operates as a form of managed access. NICE has the option to recommend for use within the CDF when NICE considers there to be 'plausible potential' (undefined) for a drug to satisfy the criteria for routine commissioning (i.e. cost-effective), but where there is remaining clinical uncertainty. CDF provides access for patients that is in line with the NICE appraisal. Funding within the CDF includes a managed access agreement, reached between NHSE and the company, which is expected to typically last around two years. The commercial element of the agreement between the company and NHSE is expected to bring the cost-effectiveness into the normal ranges used by NICE, £20,000 to £30,000 cost per QALY or up to £50,000 per QALY for treatments at the end of life. The CDF includes an expenditure control mechanism which would allow NHSE to seek rebates from companies should the CDF, funded up to £340million, become overspent. During the time a drug is on the CDF additional evidence is collected (although that need not be real world evidence, it can come from ongoing clinical trials), which can then be used to inform a NICE review.[xxvi] The CDF has historically been particularly important for access to blood cancer treatments, and the current list (as at 27 May 2020) includes over 20 blood cancer indications.[3]

The CDF is due to change into an Innovative Medicines Fund, with funding rising from £340million a year, to £500million and to cover more than just cancer treatments.[xxvii]

[3] A list is available from NHS England and is available at: **https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/**

In Scotland there is a New Medicines Fund that funds treatments for people with rare or end-of-life conditions.[xxviii] [4] The fund is supported with payments that pharmaceutical company members of the Voluntary Scheme for Branded Medicines Pricing and Access (Voluntary Scheme)[xxix] make to the Department of Health and Social Care (DHSC), who then allocate funds across the devolved nations.[xxx]

3.8 There is controversy surrounding how HTA agencies make recommendations

The ways that UK HTA agencies make their decisions has been controversial; NICE in particular has been subject to much debate.[xxxi, xxxii, xxxiii] They are also changing over time. NICE, for example, has been reviewing the methods it uses when it makes recommendations during 2019 and into 2020.[xxxiv, xxxv]

The NICE methods review is covering a broad range of areas, including modifiers used in decision making (essentially additional factors that can be taken into account that are not easy to accommodate within the usual approach to clinical and economic evidence), uncertainty, and how data analytics and real-world evidence can be used. Cancer52 has highlighted how NICE's only explicit modifier for the cost per Quality Adjusted Life Year (QALY) – a central part of NICE's decision-making – relates to life extending end of life treatments.[xxxvi] That contrasts to the SMC who have a number of modifiers including orphan designation as well as possible bridging to another definitive therapy (e.g. bone marrow transplantation).[xxxvii]

Also in scope for the NICE methods review are the criteria for topics to go into the Highly Specialised Technology (HST) programme.[xxxviii] The HST criterion are:[xxxix]

- The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS
- The target patient group is distinct for clinical reasons
- The condition is chronic and severely disabling
- The technology is expected to be used exclusively in the context of a highly specialised service
- The technology is likely to have a very high acquisition cost
- The technology has the potential for life-long use
- The need for national commissioning of the technology is significant

The HST programme is for treatments for very rare conditions. NICE is currently funded to deliver three HST appraisals each year. NICE has stated that they do not intend that any revised wording for the criteria will increase or decrease the number of HST topics.[xl]

A public consultation of changes to the NICE methods is expected during the autumn of 2020 to seek stakeholders' views and to finalise any proposed changes, ready for implementation from 2021 onwards.[xli]

[4] Desk research did not identify sources which listed which treatments are funded in the New Medicines Fund in Scotland.

3.9 HTA in the UK has been changing in the last three years

3.9.1 Changes at NICE

In the last three years NICE has been expanding the offer for engagement with companies. NICE added a Preliminary Independent Model Advice (PRIMA) service in 2017 to help quality assure health economic models that companies submit as part of the NICE TA programme.[xlii] This service is in addition to the early scientific advice service and Office of Market Access (OMA) that NICE also offers.[xliii, xliv] OMA includes engagement with NHS stakeholders.

NICE Scientific Advice is also working with the Ethical Medicines Industry Group (EMIG) – a multi-stakeholder network and trade industry association – on a collaborative programme. The aim of the programme is to bring greater understanding of the services NICE offers the life sciences industry.[xlv] NICE's advice has also included advice on patient preference study design.[xlvi]

The payer in England noted that there have been efforts to improve engagement and that this should feed into faster guidance from NICE. They said:

"NICE has speeded up its appraisals, they've brought forward engagement. If companies play by the rules, then access should have been speeded up."

Payer, England

3.9.2 Changes at the SMC

The SMC has also made changes to its approach. This includes the introduction in 2020 of a fast-track resubmission process for resubmissions within three months of the original SMC decision where the change is a new or improved Patient Access Scheme (PAS). PAS can provide access usually with a confidential price discount that enables the drug to be cost-effective. The fast track process should provide an overall assessment timeline of 14 weeks.[xlvii] Late in 2018, a new approach was introduced for rare conditions – affecting less than 1 in 50,000 people – which allows for three years of availability in Scotland allowing information on its effectiveness to be gathered.[xlviii] The first decisions using this approach have been made, and they also included the Patient and Clinician Engagement (PACE) process (discussed further later).[xlix]

In Scotland, the Scottish Health and Sport Committee opened an inquiry into medicines in September 2019, including purchasing, prescribing, dispensing and consumption.[l] A meeting was held in January 2020, and the inquiry is ongoing.[li]

3.10 HTA will influence future access to treatments

There are ongoing appraisals in blood cancer. A review of NICE appraisals (including HSTs) in development as at 21 July 2020 identified 70 appraisals ongoing in blood cancer (16% of 449 ongoing appraisals).[5] Twenty-six of the appraisals are for treatments used in combination. Sixteen unique products for blood cancer are being appraised multiple times (including outside of blood cancer), because they are used for different indications and/or in different places in the treatment pathway (nine in two appraisals, three in three appraisals, two in five appraisals, one in 25 appraisals and one in 37 appraisals).

[5] Primary analysis of data downloaded on the 21 July 2020 from **https://www.nice.org.uk/guidance/indevelopment?type=hst,ta**

3.11 HTA is just one influence on access to treatments

It is not just the role of NICE and other HTA agencies that influence access to treatments. The ways in which the NHS agencies that are responsible for budgets, such as NHSE who pays for much of cancer care, work can influence access too.[lii]

NHSE published a consultation on a new commercial framework in November 2019 which sets out the ambitions of NHSE to achieve even better value for money as well as speed up access. The consultation closed on the 10 January 2020.[liii, liv, lv] At the time of writing, the framework has not yet been finalised and remains untested. The payer in England highlighted that in practice the commercial framework is not new; rather it reflects the Voluntary Scheme. They said:

"It's really just clarified what's in the voluntary scheme."

Payer, England

It can add time if NHS England needs to agree a commercial agreement with a company. Albeit being before the commercial framework was published, the time taken to conclude a new commercial deal on the use of lenalidomide maintenance for the treatment of myeloma patients following HDT-SCT held up a NICE submission (so too did the company not having the data needed for the NICE submission).[lvi]

It's unclear how much NHSE engages early with companies whose products are/have been through NICE. In November 2019, a response to a Freedom of Information request to NHSE suggested that NHS had not conducted any early engagement for products that had been through the TA or HST programme at NICE. NHSE defined early engagement as "engaging taking place prior to the commencement, or at an early stage, of the NICE appraisal process."[lvii]

3.12 The price of treatments plays a role in access to treatments

It should also be recognised that there is an ongoing debate about the impact of price on innovation. Whilst in theory there is a balance to strike between price and innovation, industry can be criticised for charging too high prices, and payers can be criticised for extracting discounts.[lviii]

According to the academic and NICE committee member, price is the key to access. They said:

"Anything that comes to NICE, which is clinically effective, could get a yes immediately. Everything boils down to the price."

Academic and NICE committee member

Blood Cancer Alliance

4. THE ISSUES THAT NEED TO BE ADDRESSED TO ENSURE RAPID ACCESS TO BLOOD CANCER TREATMENTS AND OUR EVIDENCE-BASED RECOMMENDATIONS

Our recommendations are based on the evidence that we have gathered through the rapid evidence review, environmental scan and through seven one-to-one interviews with experts and the online survey of patients and carers. We draw upon the evidence to support the following 19 recommendations (in bold).

Our recommendations are for both industry and agencies who operate under the government and the legislation that they and their predecessors have determined, which reflects the views of the patients we represent (see Figure 5). Eighty-one per cent of respondents believe that the pharmaceutical industry should do more to make sure patients can access new treatments, that rises to 88 per cent for government. Collaboration is therefore vital. This is perhaps best summed up by the following comments from survey respondents:

"As an NHS patient, I understand that the cost of drugs, particularly new drugs, is a big issue. I know that there are many current trials for new therapies that could have significant beneficial results for myeloma patients. But there seem to be many restrictions that could limit access to potential new treatments. There are only 24,000 myeloma patients in the UK. Given that there is no cure for myeloma, I feel that drug companies, Government and the NHS should do much more to make what could be life-changing therapies for these patients as widely available as possible."

Survey Respondent

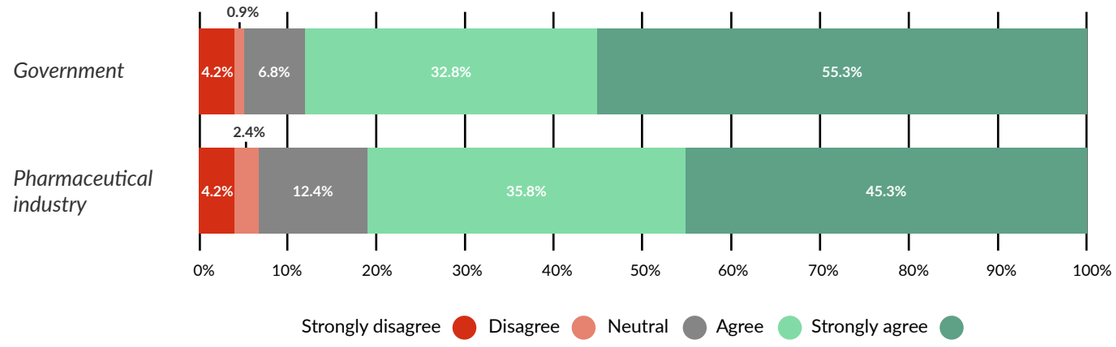
"The pharmaceutical industry and the government should work together to ensure that the best treatment can be accessed by the patient."

Survey Respondent

"I don't want tests and trials rushed. That's silly. But pharma companies need to reduce prices, and government needs to offer more funding."

Survey Respondent

Figure 5: Please indicate how far you agree or disagree with the following statement: "The government should do more to make sure that patients can access new treatments" and "The pharmaceutical industry should do more to make sure that patients can access new treatments."



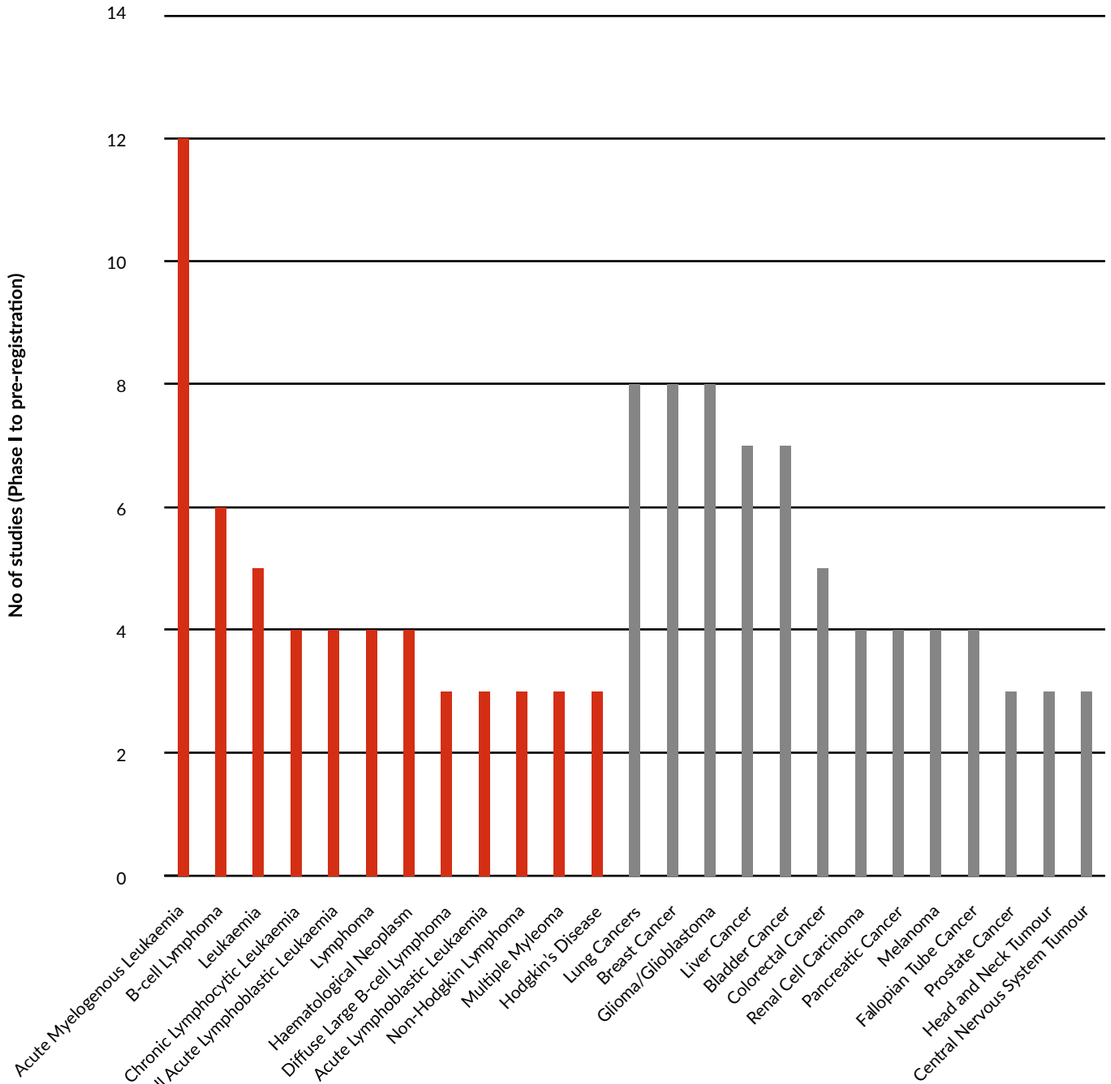
Base: 687 and 671 respectively. Note: Don't know responses have been taken out in this chart. 25 respondents for the government statement said don't know and 41 for the pharmaceutical industry statement said don't know.

4.1 The issue: New blood cancer treatments are coming through and HTA agencies and companies need to prepare for their appraisal

R&D in blood cancer in the recent past has led to a high proportion of approvals of cancer drugs by the EMA. For example, between 2000 to 2016, there were 64 drugs approved for haematological cancers, accounting for 37% of all cancer drug authorisations by the EMA.[lix]

IQVIA highlighted in their 2019 report that there are high levels of pipeline activity in oncology, including in blood cancer (see Figure 6). Trials are however complex and productivity is falling versus other therapy areas.[lx] Specialist expertise is needed in running these trials.[lxi] This research was conducted before the COVID-19 pandemic, and it may be that development could slow.

Figure 6: Top 25 cancers and the number of mechanisms targeting each



Note: Red are studies in blood cancer, grey are studies in solid tumours.
Source: Data from IQVIA. (2019). Global oncology trends 2019.
Available at: **https://www.iqvia.com/insights/the-iqvia-institute/reports/global-oncology-trends-2019**

It's often in blood cancer that the first applications of breakthrough treatments are being made, such as the first CAR T-cell therapies with their potential to 'cure.'[lxii] Research is ongoing to explore the benefits of CAR T-cell therapy in other blood cancers as well as solid tumours.[lxiii] There is also potential for patients with blood cancer to benefit from new 'agnostic' cancer treatments that have not yet been given approval.[lxiv]

Based on global R&D, IQVIA predict that there will be an increase in the number of targeted therapies for blood cancers and that R&D will also enable truly personalised treatments.[lxv]

Whilst only anecdotal, we are heartened that an HTA lead in Scotland acknowledged the promising pipeline. They said:

"From my position I am seeing a lot of medicines coming through for blood cancer and I think that they are quite innovative."

HTA lead, Scotland

A member of staff at a centre of excellence for cell and gene therapy also highlighted the activity in the blood cancer space. They said:

"There is a lot of activity going on. Blood cancer is perhaps punching above its weight in terms of R&D focus given the patient numbers."

Staff, Centre of excellence for cell and gene therapy

The challenge is likely to relate to the value for money of new treatments, as highlighted by a payer in England. They said:

"We know that many new treatments coming in the pipeline are likely to be expensive."

Payer, England

It is important to plan for the future and to ease the concerns of those with blood cancer about accessing treatments in the future; over one in ten of survey respondents are extremely concerned about accessing treatments that are in development in the future (see Figure 7).

Figure 7: Overall what would you say is your level of concern about accessing treatment(s) that are in development in the future

Answer choice		Response percent	Response total
1	Extremely concerned	11.5%	82
2	Moderately concerned	18.2%	130
3	Somewhat concerned	17.3%	123
4	Slightly concerned	20.2%	144
5	Not at all concerned	25.8%	184
6	Don't know	7.0%	50
		Answered	713

Preparing for HTA is not the responsibility for a single stakeholder group. There are already ongoing efforts to improve horizon scanning as part of the Voluntary Scheme, a restatement of commitments made in the previous scheme.[lxvi]

Horizon scanning will be needed to monitor the number of blood cancer treatments that will successfully come through development to be submitted to regulators, and from there, to be appraised by HTA agencies in the UK. All parties should have an interest in understanding the scale of the task that they will face. NHS England, as will the NHS in the devolved nations, will also benefit from understanding the potential new treatments coming through and what this will mean for delivering care.

There is also a link to the ongoing efforts being made to improve the efficiency of NICE's work so as to ensure capacity is available for future appraisals. This includes the introduction of a technical engagement step. Experience to date suggests that this has not been successful in freeing up as much committee capacity as hoped.[lxvii]

The academic and NICE committee member highlighted that there is scope for the Appraisal Committee to overrule approaches agreed through technical engagement. This could mean that further committee meetings are needed even with technical engagement. They suggested that this may be related to the competency of the NICE technical engagement team. They said:

"The technical engagement team at NICE includes the Chair or Vice Chair and lead team. Some technical engagement teams may not be good enough to make the correct call on complex issues. A NICE committee can and does overrule the technical team. What they are finding at NICE, is that they are doing a lot more work, but the number of meetings isn't going down."

Academic and NICE committee member

Some of those interviewed had experience with technical engagement. A patient representative said:

"I think it's an improvement, from one experience. Annoying ERGs and company argy bargy can be resolved before the committee. I felt it was useful and it's helpful to have additional step, heads up on where the more finalised thinking on where a treatment is going."

Patient representative, patient organisation (2)

However, they also noted that it can be difficult for patient representatives to be engaged in the technical discussion. They said:

"It's a paper-based exercise for patients. I'm not bothered about being speaking to for the sake of it, but what underlies this, the questions are all written as if we are the pharmaceutical company, they're not encouraging patients and clinicians to think about from their point of view. In technical engagement, they need to talk in a way that allows patient organisations to understand their added value in the process."

Patient representative, patient organisation (2)

NICE emailed stakeholders to advise on changes to technical engagement in June 2020. This includes replacing the technical report with an issues-based report from the Evidence Review Group (ERG). A final version of this report will be circulated and feedback collected through a structured reply form as well as consultee evidence submissions. This will give companies a right to reply to the ERG report. In addition, there will be two separate calls, one for the company and one for patient and professional experts. This latter change could be seen as a partial adoption of a PACE style of approach at NICE. The new style of technical engagement will begin for appraisals that start after the beginning of May 2020.[lxviii] However, despite the changes, the Alliance is concerned that this may still not free up sufficient capacity.

There are also opportunities, as noted earlier, for companies to engage with NICE, and NHSE.[lxix] NICE is actively promoting these fee-based services, for example, using quotes on their website collected through project feedback questionnaires.[lxx] However, unlike the EMA,[lxxi] no HTA agency includes in their reports on specific drugs whether a company sought advice. This prevents analysis that could be done externally on the impact on HTA recommendations from seeking early advice.[lxxii] It's been argued that seeing the impact on recommendations could be a strong incentive for companies to take-up early engagement opportunities.[lxxiii]

The HTA lead also highlighted how the SMC differs from NICE with respect to early engagement. SMC does not offer early engagement routinely, reflecting their more limited resourcing.

Early engagement was also highlighted by the member of staff working at a cell and gene therapy centre of excellence. They said:

"We advise the companies and the researchers that we are working with that they need to take the reimbursement part of the equation seriously from an early stage. If they don't, they may end up in a situation where the trials and evidence that they have gathered for their therapy is not sufficient to convince NICE, SMC, AWMSG that it's a good use of NHS money. As taxpayers we want the NHS to make good use of resources. It's in all our interest that they are scrutinising these things, and the onus is on companies to prepare appropriately. The evidence that they gather during clinical development need to serve not only the purposes of the marketing authorisation, which is a binary outcome, but also reimbursement, which has a continuum of outcomes, e.g. approval at a discount and/or restrictions to certain sub-populations. Failing to realise and treat that fact with the attention it deserves early on, can make reimbursement at a commercially viable price tricky."

Staff, Centre of excellence for cell and gene therapy

Recommendation 1: The Alliance calls on the Association of the British Pharmaceutical Industry (ABPI) and the Department of Health and Social Care (DHSC) to provide a public statement on progress with the commitments on horizon-scanning made in the Voluntary Scheme. The ABPI and the DHSC should assess whether current efforts are sufficient or if more work is needed and provide a public statement.

Recommendation 2: The Alliance calls on NICE and the pharmaceutical industry to develop an evidence base on the benefits of early engagement, including when patients and their representative organisations are part of the dialogue. This should include, at a minimum, publishing within final Technology Appraisal (TA) guidance whether the company has sought advice (and from which service) to bring NICE into line with the transparency provided by the European Medicines Agency (EMA). This evidence base should encourage more companies to engage, support NICE to provide a quality service, and encourage and support patients and their representatives in participating in engagement activities in the future. The SMC should consider formalising the opportunity for early engagement within their processes too.

4.2 The issue: It is vital to involve patients from R&D and beyond and for their involvement to have an impact

One-to-one interviews illustrate the need for patients to be involved in R&D. The importance of having patients involved in R&D was stressed by the HTA lead in Scotland. They said:

"It's important to involve patients right at the start of research, into access pathways, making sure that what is being developed is truly going to address unmet need. But I'm not sure how global pharma made their decisions."

HTA lead, Scotland

The same point was made by an industry representative, who also related patient involvement in R&D to helping provide evidence for later assessment by HTA agencies. They said:

"We can help them [companies] engage with patient charities, like Myeloma UK, CRUK, clinical trial networks, that can help companies to help develop the data they need for NICE assessment."

Representative of the UK pharmaceutical industry

A patient representative also made the same point.

"Companies need to ensure that what is being developed is meeting patient needs. Companies need to work with patient organisations and have the conversation with patients about what they want, rather than advantages and disbenefits of what they have got."

Patient representation, patient organisation (2)

Involving patients and the public in the HTA process can improve wider understanding of the process, promotes accountability, transparency and a more comprehensive approach to assessing value and may result in better quality decisions.[lxxiv,lxxv] Evidence has highlighted that patient considerations around individual treatment modalities, expectations on outcomes, tolerance towards side effects vs treatment effects, and psychosocial well-being vary and that this may not be obvious to other stakeholders.[lxxvi]

Whilst not in the context of an appraisal, there are novel ways being developed of capturing insights on treatment decision making and living with cancer. Crawford, Sully, Conroy et al (2020)[lxxvii] have drawn on the literature but also patient-reported information shared on YouTube by patients with acute myeloid leukaemia. The concepts reported by patients and identified through their analysis included:

- Perceived value of survival for achieving personal and/or life milestones;
- The emotional/psychological distress of their diagnosis; and
- Uncertainties about life expectancy/ prognosis.

In addition, patients expressed concerns about the lack of treatment options, the possibility of side effects and the impact of their diagnosis and treatment on relationships, daily lives and the ability to complete tasks. The authors conclude that both the literature review and the videos provided valuable and rich information, adding that understanding these insights could inform both drug development and evaluation.[lxxviii]

In an interview with a patient organisation expert they highlighted that their experience of a NICE appraisal saw them work with a patient to bring in their experience with side effects of a comparator treatment. Yet in the appraisal committee discussion this was not considered relevant. They said:

"I attended as a patient representative and I brought a patient with me. The patient didn't have direct experience of this drug, but they were able to talk about side effects of the other treatment. The Chair said lovely you are here but talking about side effects is not relevant and it won't form part of decision-making. It speaks to a broader point: the NICE process is so concerned with clinical outcomes and cost that it is missing experience of the drug that is important to the patient. It feels like the NICE process doesn't do enough to reflect that in decision making."

Patient representative, patient organisation (1)

The industry representative also noted that committees at NICE have members whose views differ with respect to patient involvement. They said:

"NICE is, in general, in favour of having patients describe their condition and how technology can help. There are others in NICE committees who don't that share that view. They don't see patient as important as they should."

Representative of the UK pharmaceutical industry

These experiences suggest that there is still work to be done to successfully bring patients into NICE's work through qualitative approaches.

Directly relevant to patient preferences being captured within NICE appraisals, Myeloma UK commissioned work on capturing patient preferences from NICE.[lxxix] This work recognises that the patient viewpoint is essential for HTA, however consideration of patient testimony in HTA is usually qualitative. It is therefore not obvious what influence patient preferences have on decision making. This work found that there is no one size fits all solution for generating patient preference data.[lxxx] However there is scope for NICE to pilot more quantitative patient preference studies. This could potentially learn from work that has done in the regulatory field.[lxxxi]

Improving the ways in which the patient perspective is brought into NICE's appraisal work is particularly important as concerns have already been raised about reducing patient involvement in the decision-making process at NICE. Consulted upon in 2017, changes designed to increase efficiency at NICE mean that patient experts (and clinician experts) are no longer automatically invited to appraisal committee meetings.[lxxxii] The Alliance's experience is that NICE staff will actively outreach to ensure attendance at the first committee meeting, but patient experts are not automatically invited to subsequent committee meetings. The direction of travel is also against positive steps taken by NICE in the past.[lxxxiii] This includes work NICE consulted on in improving how patients and the public can help develop NICE guidance and standards in 2016. Changes consulted upon included the introduction of a formal feedback mechanism giving people clear information about how NICE took their contribution into account.[lxxxiv] The Alliance understands that the changes arising from this consultation were to be implemented in 2020. NICE has been continuing to review patient involvement, including running a survey run during 2019. The results of the survey will be published as part of the wider NICE review with the consultation papers.[lxxxv]

PACE in Scotland has been highlighted by the HTA lead in Scotland. PACE is an additional opportunity for patient (and clinician) engagement for treatments used at the end of life and orphan treatments. If requested by the

company, PACE includes a meeting between patient representatives, clinicians and the SMC and results in a consensus statement that is then made available to the committee at the SMC who makes the final recommendation. It can add between 1 and 3 months to the timetable for an SMC recommendation. PACE is seen as a complement to the conventional clinical and economic evidence.[lxxxvi]

An SMC evaluation of 28 PACE processes concluded that PACE allows SMC decision-makers to take into account aspects of quality of life described in PACE that may not be fully captured in conventional quality of life instruments.[lxxxvii] SMC has also looked retrospectively at the impact on decisions; 87 medicines included PACE between August 2014 and 2017, the majority were for cancer, and the PACE acceptance rate was 77 per cent versus 48 per cent before the introduction of PACE.[lxxxviii]

The HTA lead in Scotland explained their view on the PACE process:

"PACE is not perfect by any means, but it has allowed the SMC to get a much better picture for what matters to patients and their families. It's been extremely positive."

HTA lead, Scotland

A patient expert highlighted the importance of learning between HTA agencies. They said:

"There are positive lessons from the SMC. NICE need to be open to learning from our friends across the border."

Patient representative, patient organisation (1)

Given that the June 2020 announced changes to NICE technical engagement bring in elements of PACE, through allowing for a discussion between NICE and clinical and patient experts, the Alliance believes the latest changes to technical engagement bed down before there is consideration of NICE adopting more fully the PACE style of approach. However, there are other steps that should be taken.

Recommendation 3: NICE should set out a programme to explore how to use quantitative patient preferences as part of NICE decision-making. The Alliance calls for further research to explore how quantitative patient preferences could be incorporated into economic modelling. The research should be published to enable other HTA agencies and stakeholders to learn from it.

Recommendation 4: The Alliance calls on industry, in collaboration with patients and their representative organisations, to develop an evidence base on the benefits of early engagement with patients and their representative organisations in industry R&D. This should include independent researchers. This evidence base should encourage more companies to engage patients and their representative organisations in R&D and encourage and support patients and their representatives in participating in engagement activities in the future. The research should be published to enable companies to learn from it and accelerate the involvement of patients.

Recommendation 5: NICE and SMC should develop an evidence base on their approaches to involving patients and their representatives with a focus on the difference it makes to decisions. At NICE this should include the involvement of patients and their representative organisations as part of the technical engagement step in addition to the other ways the patient perspective is brought into appraisals. Generation of this evidence base should include not only patients and their representative organisations, but also bring in independent researchers. This evidence base should encourage more patients and patient organisations to engage and encourage and support patients and their representatives in participating in HTA activities in the future. The research should be published to enable other HTA agencies to learn from it and to enable patient groups to learn how best to engage.

4.3 The issue: Modifiers play a role in HTA but need revisiting

NICE already operates with an explicit modifier with flexibilities for treatments given at the end of life (EoL). NICE's policy on end of life allows for the acceptance of less cost-effective treatments when they meet the criterion that treatments are for those patients who have a short life expectancy (usually less than 24 months) and treatments that offer an extension to life (normally of at least an additional three months).[lxxxix] SMC too has modifiers, including end of life and rarity.[xc] In blood cancer, Walton, Sharif, Simmonds et al (2019)[xci] have suggested that in the context of potential cures – such as tisagenlecleucel (Kymriah) - that there is difficulty in interpreting EoL criteria (which were not applied in the appraisal, following discussion), and the valuation of cure versus extension to life. The authors recommend that there is further clarification of NICE's position in such situations to aid in delivering consistency and equity in decision-making. Alliance members experience includes seeing NICE and academics debate the interpretation of End of Life criteria, particularly with respect to whether the criteria should be defined in terms of median or mean extensions to life where the treatment acts as a bridge to stem cell transplant.

There is also an ongoing debate about the scope of value that should be considered in HTA[xcii] – some of which could perhaps be used as modifiers too - for example, how far hope is included in HTA. Hope resonates both for cancer generally and for those with blood cancer in particular. A survey of just over 2000 members of the British public, undertaken during 2019, has found that for 76 per cent of respondents, hearing about new cancer treatments gives them hope about the future.[xciii] We found that hope was important to blood cancer patients and their carers' as illustrated by a comment from a survey respondent who said:

"I hope with more research and trials they can find a cure for myeloma. Everyone needs that hope."

Survey respondent

Whilst not directly applicable to UK cancer patients, research has found that cancer patients have a preference for 'hopeful gambles' (treatments that have a wider 'spread' of outcomes that offer the potential of a longer period of survival). This is not routinely considered in HTA.[xciv] There is also a wider debate on the objectives of health care and if they go beyond health gain; if so a number of aspects could then be relevant such as burden of illness and unmet need and hope is also amongst them.[xcv, cxvi, xcvii] This could mean adaptation to the practice of using cost-effectiveness thresholds.[xcviii]

In a review of HTA cost-effectiveness thresholds and modifiers, the Office of Health Economics (OHE) found that two main modifiers are used: severity and rarity.[xcix] Instead of a modifier, NICE has a separate approach for treatments for very rare conditions. The NICE HST programme includes a wider number of considerations that inform decisions than the TA programme:[c]

- nature of the condition (disease morbidity, impact of the disease on quality of life, extent and nature of current treatment options)
- impact of the new technology (published and unpublished clinical evidence, overall magnitude of health benefits to patients, and when relevant carers)
- cost to the NHS and personal social services (PSS) (number of eligible patients, expected uptake, opportunities for resource savings, estimated budget impact)

- value for money (technical, productive and allocative efficiency)
- impact of the technology beyond direct health benefits (costs and benefits incurred outside the NHS and PSS
- costs borne by other government bodies and costs to patients not reimbursed by the NHS, estimate of time spent by carer, impact of the technology on innovation in the UK)

The academic and member of a NICE committee also highlighted that there is the option for a Highly Specialised Technology (HST) appraisal which does have some allowance for more limited evidence; that may not be able to counter the high price however. They said:

"If it's truly an ultra-orphan treatment then it should go to HST. That's associated with higher cost per QALY threshold; so companies, for the same evidence, can charge more. With HSTs everyone is aware that there is less evidence; there is leeway for not having an RCT with 500 patients in each arm. That is taken into consideration. The trouble is that the R&D cost is so high, price you might need per patient is prohibitive."

Patient representative, patient organisation (1)

The Alliance see these as modifiers too, albeit modifiers that are only limited to those treatments that go through the HST process. As the OHE has noted, not all interventions in the ultra-rare category go through the HST programme.[ci] In blood cancer there are very small patient populations; for example, 120 people eligible for treatment with inotuzumab ozogamicin (Besponsa) for treating relapsed or refractory B-cell acute lymphoblastic leukaemia.[cii] The Alliance is also aware of an ongoing appraisal of midosturin for treating advanced systemic mastocytosis (ID1573) where the patient numbers are very small.[ciii]

In constrast, the following estimates of eligible patient populations for treatments appraised to date under HST include:[6]

- 86 patients with iInherited retinal dystrophies (IRDs) eligible for treatment with cerliponase alfa (Brineura) (HST12)
- 50 to 100 patients with type 1 Gaucher disease eligible for treatment with eliglustat (Cerdelga) (HST5)
- 142 patients with fabry disease eligible for treatment with migalastat (Galafold) (HST4)
- 74 to 77 patients with mucopolysaccharidosis type Iva eligible for treatment with elosulfase alfa (Vimizim) (HST2)

Whilst the size of the patient population is only one of the criteria for HST, it is nevertheless concerning that there appears to be an inconsistency in what is small enough for HST, or large enough for the TA programme.

The Alliance is aware that modifiers are an area that NICE is looking at as part of their review, as well as the criteria for HST.

Recommendation 6: The Alliance calls on NICE to bring in a wider range of modifiers into their deliberations. We do not specify them here as NICE's ongoing work is looking into modifiers. We do however note the ongoing work of Cancer52 who have called for more modifiers, including rarity, to be used by NICE.

[6] Based upon review of all 12 final pieces of HST guidance available from the nice website, available at: **https://www.nice.org.uk/guidance/published?type=hst**. Estimates of the number of eligible patients in England are not available in the other pieces of guidance.

Recommendation 7: NICE should clarify the criteria (e.g. the size of the patient population that is considered small enough to qualify for the HST programme) as part of their review. Flexibility is needed too with respect to which treatments can go through the HST programme to ensure treatments for rare blood cancers are not disadvantaged by the Single Technology Appraisal (STA) process which takes a narrower perspective than the HST programme and does not allow for higher cost per QALYs.

4.4 The issue: The CDF has enabled access for blood cancer patients but a change to an Innovative Medicines Fund is causing concern for future access

Blood and bone marrow cancers have accounted for just over 1 in 4 cancer recommendations that have been made by NICE (91 recommendations from 355 in cancer from 2000/1 to 2019/20, and the 91 recommendations come from 76 Technology Appraisals).[civ 7]

A comparison of NICE recommendations made for treatments of other cancers (excluding blood and bone marrow) to just those in blood and bone marrow cancers illustrates that there are fewer positive recommendations, more optimised (where a subgroup of patients are eligible for treatment) and more recommended in the context of the CDF[8] (Figure 8).

Blood cancer treatments are often going into the CDF. This highlights the link between NICE and the reforms that are planned to the CDF, to move to an Innovative Medicines Fund. Both patient representatives highlighted the change to the Innovative Medicines Fund and questioned whether it would have enough money.

"The move to the Innovative Medicines Fund is definitely a good thing for non-cancer patients. A lot of new treatments coming through have implications for other diseases. It's important to remove this false line between cancer and other things. But I worry that there won't be enough money."

Patient representative, patient organisation (1)

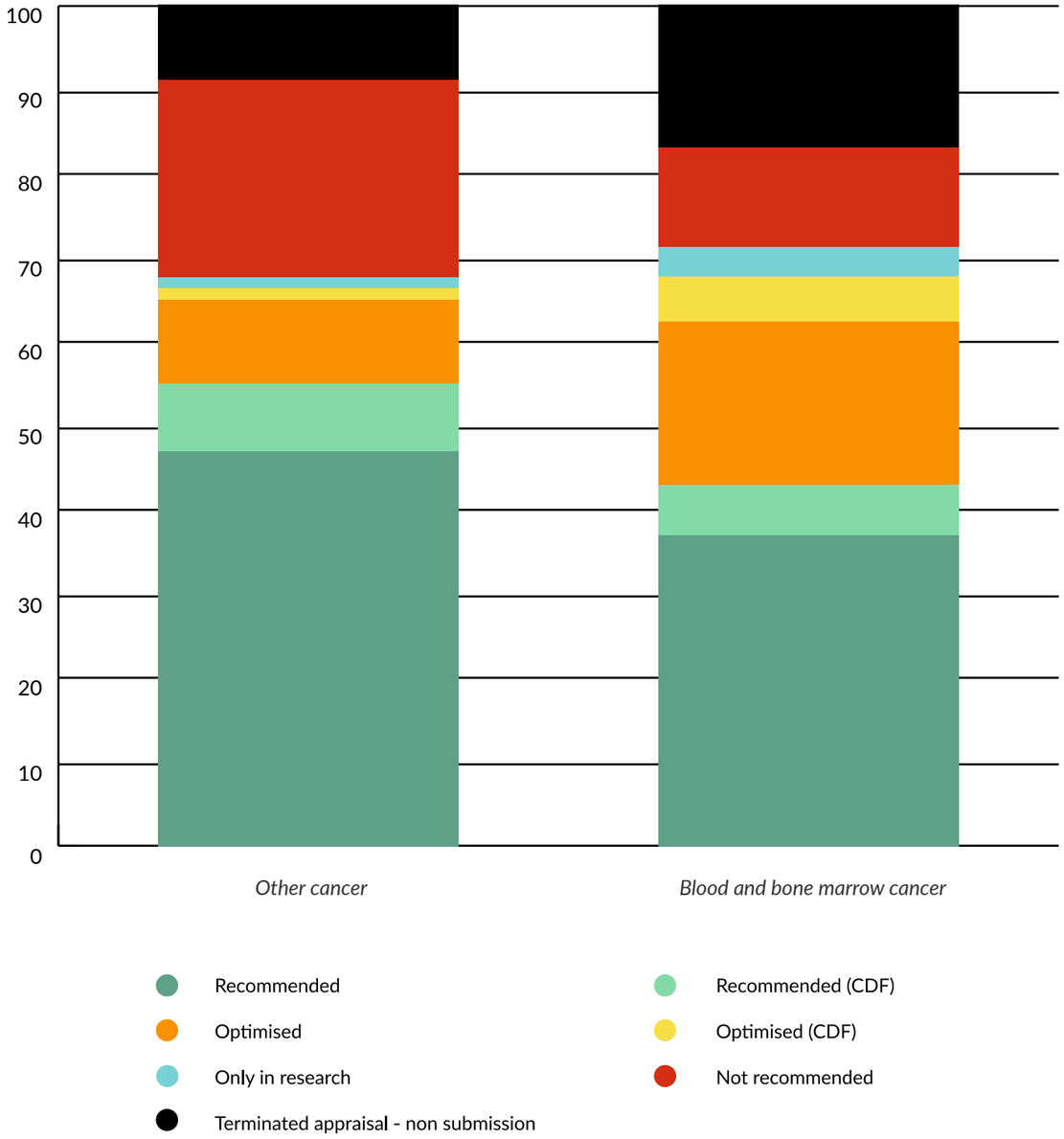
"I can see why they want to make it an Innovative Medicines Fund, I recognise that they want to encourage promising treatments, but have they increased the size of the pot enough to cover the demands on it?"

Patient representative, patient organisation (2)

[7] We have not been able to conduct the same analysis of SMC recommendations because unlike NICE, there is not an easy to access excel based source of information. Gathering data from separate webpages on the SMC website would require more resources than has been available to support this project. The same is true for AWMSG although we would not expect the AWMSG to have conducted as many appraisals as NICE given the relationship between the agencies.

[8] This includes both recommended in the CDF as well as optimised in the CDF.

Figure 8: NICE recommendations in other cancers and in blood and bone marrow cancers, 2000/1 to 2019/20



Source: Analysis of NICE data. There were 355 recommendations for all cancers, 91 of which are for blood and bone marrow cancer.

The pharmaceutical industry representative noted that there could be funding made available for the Innovative Medicines Fund from the monies paid by companies under the Voluntary Scheme. They said:

"Rebates should go into a medicines fund that is independently operated. Industry can pay for it."

Representative of the UK pharmaceutical industry

Recommendation 8: The Alliance is seeking reassurance from the Department of Health and Social Care that funding for the Innovative Medicines Fund will be sufficient so as not to disadvantage blood cancer patients – and other cancer patients – from accessing treatments that would otherwise have been available through the CDF before the move to an Innovative Medicines Fund.

4.5 The issue: Uncertainties are a common feature in the evidence base for blood cancer treatments at the time of appraisal and real-world evidence could help

The rapid evidence review identified a number of academic papers that provide the Evidence Review Group (ERG) perspective of a NICE appraisal. ERGs are external academic organisations, independent of NICE, who produce a review of the evidence submission from the company. These papers highlighted the challenge in the evidence base for blood cancer treatments; small trials and/or lack of control arms, proxies for comparators or immature survival data noted in recent appraisals by NICE. For example:

- In the appraisal of azacytidine (Vidaza) for treating acute myeloid leukaemia with more than 30% bone marrow blasts (TA399, published in July 2016), the appraisal was based upon a single open-label randomised controlled trial, comparing azacytidine to a composite comparator of treatments available in the NHS.[cv] NICE did not recommend azacytidine.

- The clinical evidence for ponatinib (Iclusig) for treating chronic myeloid leukaemia (TA451, published in June 2017) came from a phase II single-arm open-label multicentre non-comparative study.[cvi] NICE recommended ponatinib with a Patient Access Scheme.

- The NICE appraisal of obinutuzumab (Gazyva) with bendamustine for treating follicular lymphoma refractory to rituximab (TA472, published in August 2017) drew on immature data, progression free survival, from a pivotal trial, comparing obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance in comparison to bendamustine monotherapy.[cvii]

- The NICE appraisal of pomalidomide (Imnovig) with dexamethasone for treating relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib (TA427, published in January 2017) drew on an RCT which included high-dose dexamethasone as a proxy for conventional chemotherapy.[cviii] NICE recommended pomalidomide with a Patient Access Scheme.

- The NICE appraisal of obinutuzumab (Gaxyva) with bendamustine for treating follicular lymphoma refractory to rituximab (TA472, published in August 2017) drew on progression free survival

and safety evidence came from a pivotal trial, comparing obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance in comparison to bendamustine monotherapy. Overall survival data was immature.[cix]

- The appraisal of venetoclax (Venclexta) for treating chronic lymphocytic leukaemia (TA487, published November 2017) used evidence from three single-arm trials which included differences in terms of the presence of the 17p deletion/TP53 chromosomal abnormalities as well as expositive to B-cell receptor inhibitor therapy and small sample sizes.[cx] NICE recommended venetoclax for use in the CDF.

- The NICE appraisal of ibrutinib (Imbruvica) for treating relapsed or refractory mantel cell lymphoma (TA502, published January 2018) drew on an RCT that compared ibrutinib with temsirolimus and from two single-arm studies.[cxi] NICE recommended ibrutinib with a commercial access agreement.

- The main clinical evidence came from an RCT with 771 patients in the appraisal of ixazomib (Ninlaro) for relapsed or refractory multiple myeloma (TA505, published February 2018).[cxii] NICE recommended use in the CDF with a commercial access agreement.

- The NICE appraisal of obinutuzumab (Gazyvaro) in combination with chemotherapy for the first line treatment of patients with advanced follicular lymphoma (TA513, published March 2018) drew on two phase III randomised open-label studies.[cxiii] NICE recommended use of obinutuzumab for patients with advanced follicular lymphoma and a Follicular Lymphoma International Predictive Index (FLIPI) score of two or more.

- The NICE appraisal of pembrolizumab (Keytruda) for treating relapsed or refractory classical Hodgkin lymphoma (TA540, published September 2018) in two patient populations; patients who did and did not receive prior autologous stem cell transplant. Indirect comparisons were used given a lack of studies directly comparing pembrolizumab with single or combination chemotherapy.[cxiv] NICE did not recommend pembrolizumab in those who have received a transplant but recommended use, in the CDF, for those who did not.

- NICE appraisal of tisagenlecleucel (Kymriah) – a CAR T cell therapy - for the treatment of relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (TA554, published December 2018) was based upon three single-arm phase II studies that demonstrated extensions in event-free survival and overall survival in comparison to historical control datasets where treatment was blinatumomab and salvage chemotherapy.[cxv] NICE recommended use in the CDF and will draw on the ongoing ELIANA trial to inform a review in the future.

A range of strategies can be employed in response to limited evidence and uncertainties; indirect comparisons (used in TA451,TA427, TA540, TA502) and network meta-analyses (used in TA505, TA502) as well as the use of Patient Access Schemes/ commercial access schemes (in TA451, TA427, TA472) and in some cases, time limited funding in the CDF (in TA487, TA505, TA472, TA540).

Research has explored how real-world evidence, in the case of lenalidomide used in myelodysplastic syndrome deletion 5q (TA322, published in September 2014), can help overcome the lack of mature data from trials at the time of submission to HTA. Real-world evidence as published in the literature was used to help confirm key findings using surrogate outcomes, including time on treatment and use of transfusion dependency as a surrogate for overall survival. The authors practical advice is that there is a search for real-world evidence before submissions are made to HTA agencies. The authors also acknowledge that this approach may not be generalisable to other treatments since real-world data may not always be available.[cxvi] Post approval and/or appraisal RWE can become available.

NICE has published a statement of intent to increase and extend the use of data in their work. This includes the use of electronic health record data, real world data, and relevant data collected outside of the context of traditional trials.[cxvii]

The HTA lead in Scotland also noted the use of real-world data in SMC submissions, explaining that it is not widely included. They said:

"The SMC has a position in their methods; real world data can be included in company submissions. It's a much talked about but the SMC doesn't see a great deal of in practice."

HTA lead, Scotland

Quality of real-world data and evidence emerged from discussion with a patient expert. They noted that their experience of an appraisal included consideration of registry data. The data was not considered by the company to be sufficiently robust to be drawn upon in the appraisal. They said:

"The company had trial data outside of the UK. They then tried to get comparative data from registry. But they decided it was not going to work."

Patient representative, patient organisation (1)

The pharmaceutical industry representative suggested that further guidance could be helpful to companies so that they will know what will be acceptable for HTA with respective to real world data and evidence. They said:

"We need a standard on real world data and real-world evidence."

Representative of the UK pharmaceutical industry

Recommendation 9: The Alliance calls on companies to proactively look for real-world evidence that could be used in their submissions to HTA agencies. Companies should provide a statement in their submission that they have done so.

Recommendation 10: The Alliance calls on HTA agencies to set out more detailed guidance to aid companies in considering what real-world evidence, including features of registries and patient group surveys, will be acceptable to support submissions. This should go beyond the submission if appropriate, to help guide real world evidence generation that can be conducted to address uncertainties at the time of appraisal. This will help send signals to all those involved in setting up and reforming existing real-world data sources about the needs of HTA agencies.

4.6 The issue: The CDF has enabled access for blood cancer patients but the evidence that NICE needs to counter uncertainty at the time of appraisal is not always being collected

The CDF is seen by some as the main approach to review evidence as it emerges according to the payer in England. They said:

"The CDF has provided an important mechanism to review value for money as experience develops. There are downsides of real world evidence, all kinds of biases can result. But there are techniques becoming available to address that."

Payer, England

The CDF is seen favourably too by the member of staff at the centre for excellence for cell and gene therapy. They said:

"The CDF has helped. I've been involved in recommending a lot of drugs go to CDF. It's got to be plausibly cost effective at the price being offered. When they [companies] come with immature data at NICE, we're uncertain about it. The treatment could be better, or a lot worse."

Academic and NICE committee member

A patient representative also highlighted the CDF and its role in generating evidence. They said:

"The CDF is the biggest experience we have with real-world data and evidence."

Patient representative, patient organisation (2)

The HTA lead also highlighted how the SMC is planning to roll out conditional acceptance, which had been delayed by COVID-19. This will allow the SMC to accept a medicine that has been given a conditional marketing authorisation, on an interim basis, and for the company to submit new evidence for a review in the future. There is also ongoing work on the Cancer Medicines Outcomes Programme (CMOP). This will enable comparison of real-world data with trial evidence. A pilot is ongoing.

Grimm, Fayter, Ramaeker et al (2019)[cxviii] highlight that, in general, more appraisals are being undertaken drawing upon single-arm studies and without mature data and suggest that guidelines could be useful to provide guidance on the circumstances where non-randomised controlled trial evidence is acceptable and would be useful. Research has suggested that in some cases, including in blood cancer, there is not always a match between the uncertainty identified by NICE and the data being collected.[cxix]

It's therefore likely that future treatments will face the same challenges of a limited evidence base and reinforces the need for the CDF to provide an opportunity for evidence to be generated on blood cancer treatments to support a fuller appraisal by NICE in due course. Yet it is concerning that the CDF may not be enabling the collection of evidence that will help to address the uncertainties identified by NICE. This could be storing up future access challenges.

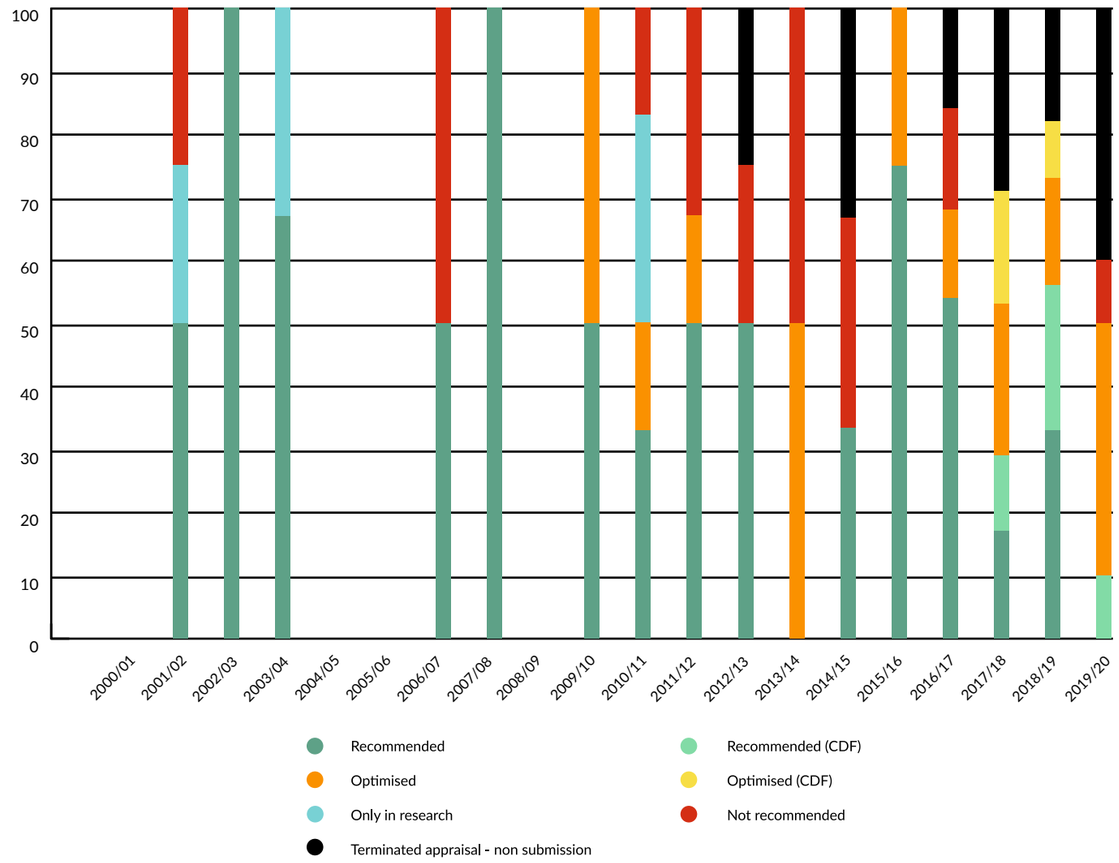
Recommendation 11: The Alliance calls on NICE and NHSE to ensure that there is a clear link between the main clinical uncertainties identified at the time of the first appraisal by NICE and the clinical data that is generated during the time that a treatment is within the CDF. Agreements reached with companies should ensure that the main clinical uncertainties are addressed in the evidence generation that they are responsible for, if appropriate. The DHSC, as sponsor of both NICE and NHSE, should raise this as part of its work to hold both agencies to account and this should be demonstrated in published meeting minutes.

Recommendation 12: Guidance on plausible potential to be cost-effective should be published by NHS England. This will aid company planning and help patient groups by informing their input into discussions on potential treatments to go into the CDF.

4.7 The issue: Non-submissions are rising in blood cancer

Submitting to NICE is voluntary for companies. The analysis of NICE recommendations has illustrated that non-submissions have been increasing in recent years (Figure 9). A key example of this in blood cancer is the non-submission of Ibrutinib as a first line treatment for chronic lymphocytic leukaemia.

Figure 9: NICE recommendations in blood and bone marrow cancers, by year 2000/1 to 2019/20



Source: Analysis of NICE data.

NHS England has taken the position that, where NICE cannot make a recommendation to the NHS due to non-submission by the company, they will not routinely commission the treatment. This is to avoid circumventing of the NICE process. Only in exceptional cases will NHS England consider interim commissioning; where the company have indicated that they are willing to submit evidence to NICE, where timescales may result in harm to the patient population and there is sufficient evidence of significant clinical benefit that NHS England would want to commission the medicine before the publication of final guidance.[cxx]

The payer in England noted that in their experience the majority of companies do engage. They said:

"We do see a difference in companies. Some companies know the rules and are prepared to price responsibly and then there is access. Others don't want to play that game. Effectively that's when delays occur. Presumably companies have done their sums and decided not to engage; it's a commercial decision when they don't provide a submission to NICE. Most companies are able to participate and do engage. The question is what's different about those companies who choose not to? I don't have an answer for that."

Payer, England

Non-submissions are also an issue in Scotland. The HTA lead told us that:

"I know that there are certainly a number of medicines where the company have not brought a submission to the SMC. It's not always clear why that is. It's an intention [at the SMC] to not have that situation. I think that there are several things that come through for blood cancer, which are regarded as innovative, yet the company has not made a submission. It might be around the difficulties of making the case for cost-effectiveness, or not anticipating that there will be uptake. The lack of multi-indication pricing is an ongoing issue. It's a challenge and we would like to make sure that there aren't non-submissions; it's not in the patients' best interest if companies don't go through the SMC process."

HTA lead, Scotland

The lack of multi-indication pricing has also been raised by a patient representative. They said:

"The bit things get stuck at is the lack of multi-indication pricing. There can be problems when a treatment is licensed in several indications, and companies are reluctant to pursue certain indications because it will bring the price down across the board. We need companies to be patient centred and price responsibly but the commercial framework could be more flexible to unlock this."

Patient representative, patient organisation (2)

The drivers of non-submissions appear to be a multi-factorial and are not likely to be solved by HTA agencies working alone. This is particularly the case with multi-indication pricing. Currently multi-indication pricing – where the price for the same treatment is different according to the indication it is used in – is not widely available in the UK. It is explicitly referenced in the Voluntary Scheme which states that "the health service in England will continue to adopt uniform pricing by medicine" albeit there is scope for flexibility in exceptional cases.[cxxi] Based upon the interview with the HTA lead in Scotland the lack of indication-based pricing is a real challenge. They said:

"There feels like there is a bit of a stalemate on multi-indication pricing and combination pricing. The SMC recognise the challenges for companies, but at the same time, there are challenges for health boards to implement different prices for different indications or use. It's incumbent for those in HTA and in pharma to address these thorny issues and get solutions in patient interest."

HTA lead, Scotland

Pricing of combination treatments was also a factor noted by a patient representative working at a patient organisation. They said:

"It's combinations. We know non-submissions have happened and that companies say is because of impossibility of making combinations work, when the treatments come from two different companies."

Patient representative, patient organisation (2)

Pricing in the context of combinations has been a challenge to HTA; NICE has faced the real world example of a breast cancer treatment, pertuzumab (Perjeta), that would not be cost-effective even if priced at zero during the stages of the NICE appraisal during 2013 because it was given in combination.[cxxii] The NICE Decision Support Unit (DSU) explored this issue in a 2014 report and recognised that when new treatments are given in combination with existing treatments it may be difficult to demonstrate cost-effectiveness and that they may only be cost-effective at a positive price if discounts are offered on other technologies given at the same time as the new treatment.[cxxiii] NICE has subsequently recommended pertuzumab in the context of a commercial access agreement.

Companies cannot legally discuss pricing with other companies and yet the value of treatment is a function of the pricing of the combination treatments. It is related to indication-based pricing too; the UK does not routinely permit different prices by indication, and the price when used in combination cannot be changed. Under the Voluntary Scheme there is ongoing work by the ABPI on enabling companies to engage with one another where combination therapies face challenges coming to market.[cxxiv]

The patient representative noted that they were aware that discussions on combination pricing were ongoing.

Analysis of ongoing NICE appraisals of blood cancer treatments illustrates that there are number of ongoing of appraisals for treatments that have multiple indications and/or are used in combination with other treatments. This raises the potential for non-submissions driven by the lack of indication-based pricing and/or combinations to increase in their frequency. This suggests that there is an increasing urgency to resolve these complex pricing issues.

Global implications are also likely to be at the forefront of company's decision-making with respect to making a submission according to a representative of the pharmaceutical industry. They said:

"If they don't submit it may be to do with reference pricing."

Representative of the UK pharmaceutical industry

It's also worth noting that not all stakeholders view non-submissions as a cause for concern; the academic and NICE committee member said:

"It's simple, in my view, I'm not concerned if they walk away, if the drug is not cost-effective, not going to say yes anyway as a year will reduce overall societal health."

Academic and NICE committee member

Recommendation 13: The Alliance calls for the ABPI to update on progress on combination pricing and publish a road map to adopt a solution.

Recommendation 14: The Alliance calls on all stakeholders to address the issue of multi-indication pricing. It is no longer sufficient to offer some flexibilities in exceptional circumstances; treatments with multiple indications are now common place. Where agreements have permitted multi-indication pricing these should be assessed on what can be learnt to permit wider rollout so as to provide patient access.

Recommendation 15: When it comes to treatments that are not cost-effective at zero price, for example, because of the high cost of backbone therapy a solution needs to be found to ensure that patients can access the treatment and that there is a reasonable apportionment of reward to the value being generated to those companies whose treatments are being used. NICE could explore the discount required in backbone therapies, for example. This would provide signals to the company and the NHS as to the pricing changes that are needed.

4.8 The issue: There is more potential for outcome-based payment

The notion of paying according to outcomes has emerged through discussion. The HTA lead in Scotland said:

"I'm interested in a more adaptive or life cycle approach to a new medicine, where we can assess value later, and the price can up or down, not always down. There are challenges for data collection but I'd want to get better outcomes based on data."

Payer, England

It was also raised by the member of staff at the centre for excellence in cell and gene therapies. They said:

"I would like to see a data platform able to utilise the data that is already being recorded for patients being treated in different trusts. All the data that is required to get a better view on how well things work in the real world and which could be used to tie in finances with payments for the product, all of that is collected. We can look to Italy and Spain, there are efforts to do this. I'd like to see the implementation of advanced reimbursement schemes, like outcomes based contracts. Then the health care system pays for what it gets. However there are legitimate concerns around the administration burden of implementing such schemes, so it may not make sense in every instance."

Staff, Centre of excellence for cell and gene therapy

Outcomes-based pricing was also mentioned by a patient representative. They said:

"I can see why a policy basis is increasing for outcomes-based commissioning, we have situations in cancer where drugs have sat at a price for too long, particularly on combination side. It is only right companies given almost as standard, a conditional approval, then they have to come back and show what the treatment is really delivering."

Patient representative, patient organisation (1)

There has been ongoing work to explore the feasibility of outcome-based payment for cancer medicines. It is seen as having the potential to speed up access, promote value for money and support innovation.[cxxv] Outcomes-based agreement/payment by results is also an example of a commercial arrangement included in the NHS England draft commercial framework. Such an arrangement is open only for those treatments where companies offer greater levels of health gain relative cost which means medicines that are expected to have value propositions at or below the lower end of the standard cost-effectiveness threshold range. Ongoing research is establishing the steps needed to prepare for a plot of outcome-based payment in Greater Manchester.[cxxvi]

Recommendation 16: DHSC and NHSE should state their current positions on outcome-based payment now that we are half way through the Voluntary Scheme lifetime.

Recommendation 17: All stakeholders should be actively monitoring the debate on outcome-based pricing and should pay attention to the results of the ongoing OHE research on outcome-based pricing in due course. DHSC and NHSE should formally respond to the results of the pilot.

4.9 The issue: Submissions to NICE have errors; submissions need to improve

ERGs have highlighted concerns about company's NICE submissions for blood cancer treatments, including errors or concern about how far uncertainty was explored. [cxxvii, cxxviii, cxxix, cxxx, cxxxi, cxxxii, cxxxiii, cxxxiv]

Specific examples of appraisals where ERGs identified errors include:

- Tikhonova et al (2017),[cxxxv] in the appraisal of azacytidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts (TA399, published in July 2016), noted errors in the company modelling.
- Büyükkaramikli, de Groot, Fayter et al (2018)[cxxxvi] identified errors in the company submitted model in the NICE appraisal of Imnovid (pomalidomide) with dexamethasone for treating relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib (TA427, published in January 2017).
- Armoiry, Connock, Tsertsvadze et al (2018),[cxxxvii] in the appraisal of ixazomib (Ninlaro) for relapsed or refractory multiple myeloma (TA505, published February 2018), noted that the hazard ratio was inverted in the company network meta-analysis.
- Thielen, Büyükkaramikli, Riemsma et al (2019)[cxxxviii] noted errors in the company modelling in the NICE appraisal of Gazyva (obinutuzumab) in combination with chemotherapy for the first line treatment of patients with advanced follicular lymphoma (TA513, published March 2018).[cxxxix]

- Mistry, Nduka, Connock et al (2018),[cxl] in the appraisal of Venclexta (venetoclax) for treating chronic lymphocytic leukaemia (TA561, published in February 2019), noted errors in the company's modelling.

Aside from adding to the complexity of an appraisal and the volume of materials for committees as well as stakeholders to review and deliberate upon, it can also result in delays to NICE guidance. This is because correcting and amending modelling and communicating these to NICE can lead to the need for additional committee meetings.[cxli,cxlii]

In response to the publication of a research paper highlighting technical errors and validation processes in economic models submitted to NICE during 2017, Jeanette Kusel, Director of NICE Scientific Advice noted the importance of the NICE PRIMA service to check models prior to submission.[cxliii]

At times the resulting cost-effectiveness arising from changes requested or made by the ERG can be starkly different, for example in the appraisal azacytidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts (TA399, published in July 2016), changed the base case cost per QALY of £20,648 from the company to £273,308 per QALY following critique and changes from the ERG.[cxliv] This example comes from before the introduction of a technical engagement step which was introduced in 2018 with the aim of allowing greater opportunity for NICE technical staff, the ERG and the members of the committee to seek clarification from the company, requesting further analyses, and performing their own exploratory analyses. The overall intention for this change, along with others, was to increase the capacity within the technology appraisal programme.[cxlv]

The suggestion has been made that company collaboration in pharmacoeconomic modelling could help to reduce mistakes, albeit it may take longer. Multiple myeloma is highlighted as an area where there are multiple models with very similar structure and seeking to solve very similar problems from the perspective of disease progression.[cxlvi]

Our rapid evidence review did not identify comparable papers to those from ERGs on NICE submissions. However, our interview with the HTA lead in Scotland noted challenges in the submissions that SMC receive.

"It often feels like the SMC are getting a bit of a cut and paste job in terms of what has gone to NICE."

HTA lead, Scotland

Recommendation 18: Companies and those that support them in producing models and submissions to NICE should consider using the NICE PRIMA service to help identify technical errors and improve validation processes. In all cases, companies and those that support them need to improve their processes to minimise errors and avoid causing delays.

4.10 The issue: Rapid access requires speedy collaboration

Collaboration can enable rapid access, or a lack of collaboration can hinder rapid access. In the past there has been the example of a lack of collaboration, or perhaps more of a case of re-interpretation of NICE guidance, by NHSE. In the case of access to ibrutinib (Imbruvica) for people with chronic lymphocytic leukaemia.[cxlvii] Around 200 people could not access ibrutinib because of NHS England restrictions that related to age criteria that were not in the NICE guidance.[cxlviii] A collaboration between CLL Support, Leukaemia Care and Blood Cancer UK (formerly known as Bloodwise) worked to counter these restrictions.[cxlix] Janssen also agreed to fund some of the additional costs generated by removing age restrictions.[cl] There were concerns expressed then that this might not be an isolated care.[cli] It should be noted here that Ibrutinib remains unavailable as a first line treatment for CLL, due to an issue of non-submission as outlined in section 4.7.

This contrasts to the case of CAR T-cell therapies. The member of staff at a centre for excellence for cell and gene therapy highlighted how collaboration had aided speedy access. They said:

"There have been some encouraging developments for CAR T-cell therapies. They were approved by NICE within 10 days of getting marketing authorisation from EMA. NICE and NHS England should be commended for their fast approval; there was a lot of resource in meeting with stakeholders, pre-empting the dawn of this new wave of therapies. This enabled patients to gain access in record time. I'd never seen that before."

Staff, Centre of excellence for cell and gene therapy

It will be important for the spirit of collaboration to be used in reaching commercial agreements with companies. The aim should be for an agreement to be reached speedily that can meet both sides' needs. Lengthy negotiations, as seen between the company and NHS England, on the use of lenalidomide maintenance for the treatment of myeloma patients following HDT-SCT, should avoid holding up the NICE submission, as it did in this case. Another factor was the the company not having the data needed for the NICE submission.[cliii]

Collaboration that enables fast access is possible, even during a global pandemic. This has been illustrated an access deal announced on the 30 June 2020 between NHSE and Vertex pharmaceuticals. The agreement was reached for a triple treatment (ivacaftor, texacaftor and elexacaftor) for cystic fibrosis before approval from the EMA and goes beyond the anticipated licence to include patients with rare mutations. Simon Stevens, NHS chief executive, highlighted that Vertex was willing to work flexibility with the NHS. The deal also includes an agreement for further data to be collected to support future appraisal by NICE. Prices could be adjusted too, following the NICE appraisal, to ensure a good deal for taxpayers. This has all the hall marks of an approach that the Alliance believes could apply for future blood cancer treatments too.[cliii]

Recommendation 19: Stakeholders have shown how they can work together to enable fast access, including through the COVID-19 pandemic, and this spirit of working together must continue and be turned into business as usual.

Blood Cancer Alliance

APPENDICES

Appendix 1: Pubmed searches

The following searches were conducted on Pubmed.

Search	Add to builder	Query	Items found	Time
#7	Add	Search (((((access OR reimbursement OR coverage OR recommendation* OR decision* OR funding OR health technology assessment OR health technology appraisal OR HTA OR economic evaluation OR cost effectiveness analys* OR cost-effectiveness analys* OR CEA OR cost utility analys* OR cost-utility analys* OR CUA OR real world data OR real-world data OR RWD OR real world evidence OR real-world evidence OR RWE))) AND ((treatment OR medicine* OR drug* OR pharmaceutical OR biological OR immunotherapy OR monoclonal OR CAR T))) AND ((blood cancer OR lymphoma OR malignant immunoproliferative disease OR myeloma OR leukaemia OR haematopoietic OR polythemia vera OR myelodysplastic syndrome))) AND ((National Institute for Health and Care Excellence OR NICE OR Scottish Medicines Consortium OR SMC OR All Wales Medicines Strategy Group OR AWMSG OR United Kingdom OR UK OR England OR Northern Ireland OR Scotland OR Wales)) Filters: Publication date from 2017/01/01; English	1243	06:09:56
#6	Add	Search (((((access OR reimbursement OR coverage OR recommendation* OR decision* OR funding OR health technology assessment OR health technology appraisal OR HTA OR economic evaluation OR cost effectiveness analys* OR cost-effectiveness analys* OR CEA OR cost utility analys* OR cost-utility analys* OR CUA OR real world data OR real-world data OR RWD OR real world evidence OR real-world evidence OR RWE))) AND ((treatment OR medicine* OR drug* OR pharmaceutical OR biological OR immunotherapy OR monoclonal OR CAR T))) AND ((blood cancer OR lymphoma OR malignant immunoproliferative disease OR myeloma OR leukaemia OR haematopoietic OR polythemia vera OR myelodysplastic syndrome))) AND ((National Institute for Health and Care Excellence OR NICE OR Scottish Medicines Consortium OR SMC OR All Wales Medicines Strategy Group OR AWMSG OR United Kingdom OR UK OR England OR Northern Ireland OR Scotland OR Wales)) Filters: Publication date from 2017/01/01	1252	06:09:51
#5	Add	Search (((((access OR reimbursement OR coverage OR recommendation* OR decision* OR funding OR health technology assessment OR health technology appraisal OR HTA OR economic evaluation OR cost effectiveness analys* OR cost-effectiveness analys* OR CEA OR cost utility analys* OR cost-utility analys* OR CUA OR real world data OR real-world data OR RWD OR real world evidence OR real-world evidence OR RWE))) AND ((treatment OR medicine* OR drug* OR pharmaceutical OR biological OR immunotherapy OR monoclonal OR CAR T))) AND ((blood cancer OR lymphoma OR malignant immunoproliferative disease OR myeloma OR leukaemia OR haematopoietic OR polythemia vera OR myelodysplastic syndrome))) AND ((National Institute for Health and Care Excellence OR NICE OR Scottish Medicines Consortium OR SMC OR All Wales Medicines Strategy Group OR AWMSG OR United Kingdom OR UK OR England OR Northern Ireland OR Scotland OR Wales))	3271	06:09:38
#4	Add	Search (National Institute for Health and Care Excellence OR NICE OR Scottish Medicines Consortium OR SMC OR All Wales Medicines Strategy Group OR AWMSG OR United Kingdom OR UK OR England OR Northern Ireland OR Scotland OR Wales)	1842630	06:09:03
#3	Add	Search (blood cancer OR lymphoma OR malignant immunoproliferative disease OR myeloma OR leukaemia OR haematopoietic OR polythemia vera OR myelodysplastic syndrome)	985331	06:07:36
#2	Add	Search (treatment OR medicine* OR drug* OR pharmaceutical OR biological OR immunotherapy OR monoclonal OR CAR T)	17632515	06:06:24
#1	Add	Search (access OR reimbursement OR coverage OR recommendation* OR decision* OR funding OR health technology assessment OR health technology appraisal OR HTA OR economic evaluation OR cost effectiveness analys* OR cost-effectiveness analys* OR CEA OR cost utility analys* OR cost-utility analys* OR CUA OR real world data OR real-world data OR RWD OR real world evidence OR real-world evidence OR RWE)	1874527	06:05:35

Date searched: 3 March 2020. 31 of the 1,243 papers identified were included based upon their relevance.

Search	Actions	Details	Query	Results	Time
#3	•••	>	Search: **(invest* AND/OR research and development AND/OR R&D AND/OR trial*) AND (blood cancer AND/OR lymphoma AND/OR malignant immunoproliferative disease AND/OR myeloma AND/OR leukaemia AND/OR haematopoietic AND/OR polycythemia vera AND/OR myelodysplastic syndrome)** Filters: **English, from 2017 - 2020**	563	08:49:02
#2	•••	>	Search: **(invest* AND/OR research and development AND/OR R&D AND/OR trial*) AND (blood cancer AND/OR lymphoma AND/OR malignant immunoproliferative disease AND/OR myeloma AND/OR leukaemia AND/OR haematopoietic AND/OR polycythemia vera AND/OR myelodysplastic syndrome)** Filters: **from 2017 - 2020**	577	08:48:53
#1	•••	>	Search: **(invest* AND/OR research and development AND/OR R&D AND/OR trial*) AND (blood cancer AND/OR lymphoma AND/OR malignant immunoproliferative disease AND/OR myeloma AND/OR leukaemia AND/OR haematopoietic AND/OR polycythemia vera AND/OR myelodysplastic syndrome)**	3,131	08:48:44

Date searched: 29 June 2020. No papers were included because they did not appear to, based on their title, cover research and development trends as a whole. Rather most studies are about guidelines, reports from individual RCTs etc.

Appendix 2: Websites searched in the environmental scan

The table below sets out all the agencies websites that have been searched.

	England	Northern Ireland	Scotland	Wales	Other geography
Parliamentary groups and committees	APPG on blood cancer APPG on children, teenagers and young adults APPG on access to medicines and medical devices Health and Social Care Committee (DHSC)	All Party Group on Cancer Committee for Health	Cancer cross party group Health and Sport Committee	Cancer Cross Party Group Health, Social Care and Sport Committee	
Government department with responsibility for health	Department of Health and Social Care (DHSC)	Department of Health	Health and Social Care	Department of Health and Social Services	
Other government departments/ initiatives	Department for Business, Energy & Industry Strategy (BEIS) Office for Life Sciences (OLS) Accelerated Access Collaborative (AAC)				
HTA agency (if applicable)	National Institute for Health and Care Excellence (NICE)		Scottish Medicines Consortium (SMC)	All Wales Medicines Strategy Group (AWMSG)	
NHS	NHS England (NHSE)	Health and Social Care Online	NHS Scotland	NHS Wales	
Industry	Association of the British Pharmaceutical Industry (ABPI) BioIndustry Association (BIA)				European Federation of Pharmaceutical Industries and Associations (EFPIA) Pharmaceutical Research and Manufacturers of America (PhRMA)
Other	Evaluate Genetic Alliance UK Health Technology Assessment International (HTAi) IQVIA Institute for Cancer Research International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Kings Fund Office of Health Economics Specialised Healthcare Alliance				

The following websites of the BCA and their membership were also searched:

- Blood Cancer Alliance
- ACLT
- Anthony Nolan
- Bloodwise/Blood Cancer UK
- CLL Support
- CML Support Group
- DKMS
- Leukaemia Care
- Leukaemia and Lymphoma NI
- Leukaemia UK
- Lymphoma Action
- MDS UK Patient Support Group
- Myeloma UK
- Race Against Blood Cancer
- WMUK

In addition, general searches were carried out in Google.

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