Thank you for agreeing to give us a statement on your organisation’s view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

### About you

**Your name:** Dr Dominic Culligan

**Name of your organisation:** and representing The Royal College of Pathologists and the BCSH.

**Are you (tick all that apply):**

- a specialist in the treatment of people with the condition for which NICE is considering this technology?  
  
  - a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?  
  
  - an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology?  If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?  
  
  - other? (please specify)
What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Myelodysplastic Syndromes (MDS) are a heterogeneous group of haematological malignancies with the shared characteristics of ineffective and dysplastic haemopoiesis and a variable tendency to progress to acute myeloid leukaemia (AML). Patients are elderly with a median age in excess of 70 years and suffer from the effects of bone marrow failure, principally anaemia. Patients die from progressive bone marrow failure or development of AML. The International Prognostic Scoring System (IPSS) stratifies patients into low risk (Low and Intermediate-1) and high risk (Intermediate-2 and High). Low risk patients have lower blast counts and fewer cytopenias and better prognostic cytogenetic results. They live longer and have a lower risk of progressing to AML. The complex pathogenesis of MDS includes acquired aberrant hypermethylation and consequent silencing of certain genes involved in blood cell growth and development. This provides a scientific rationale for the use of hypomethylating agents like azacitidine which may contribute to reversing this process.

MDS patients are managed by haematologists and the majority are cared for in district general hospitals. Until recently there have been few effective treatments available. The vast majority of patients are managed with supportive care only, based around red cell transfusions. This was emphasised by a recent French study (Kelaidi C et al. MDS in France: Results of a one-week cross-sectional survey on daily practice management in 919 patients by GFM. Blood 2008 112 abstract 2672) in which on-going or recent treatments were assessed in all MDS patients seen in clinic during a specified one week period at all GFM centres. Of the 919 patients 66.5% had received no active treatment in the last 6 months and for the high risk IPSS groups this was 72.9%. A small minority of relatively younger patients (<60-65 yrs) can be cured by allogeneic stem cell transplantation.

Some low risk patients with mild anaemia and low transfusion requirement benefit in terms of a useful rise in haemoglobin concentration following treatment with...
Erythropoietic stimulating agents (ESA) (erythropoietin and darbopoietin) with or without granulocyte-colony stimulating factor (G-CSF). Overall, about 20-40% of treated patients respond but of those with a high pre-treatment predictive score about 70% responds. There are recent cohort data suggesting a survival advantage for patients who respond to ESA therapy. However, the cost of ESA therapy is seen as prohibitive in many centres in the UK despite its recommendation in The BCSH Guideline from 2003. The NCRI UK MDS trials group is currently implementing a UK wide randomised trial of ESA versus best supportive care for low risk MDS patients (REGiM). A well defined subgroup of low risk patients carrying the cytogenetic abnormality del(5q) have been shown to have a dramatic response to the drug lenalidomide, with 67% of such patients becoming transfusion independent and the response lasting for a median of 2 years. Lenalidomide has not received a European license for this indication and is not currently available in the UK. A small cohort of relatively fit patients with low risk refractory anaemia can tolerate and respond to intensive immnosuppression with the drug anti-lymphocyte globulin (ALG).

Presently available drug treatments for high risk MDS provide no discernible survival advantage. Some high risk patients are treated with AML type intensive chemotherapy. This rarely produces prolonged remissions without consolidation with an allogeneic stem cell transplant and most experts would not offer intensive chemotherapy outside of a trial unless a subsequent transplant was an option. Some high risk patients (>10% blasts) are entered into the NCRI AML16 trial and receive experimental agents, but high risk patient with < 10% blasts are not eligible. High risk patients are frequently treated with low dose cytosine arabinoside. This is the commonest 'default treatment' for high risk MDS but produces remissions in only 10-20% and a median survival of only 4-6 months. Low dose cytosine arabinoside remains the standard comparator arm in NCRI AML 16.

Against this background azacitidine is a major advance in the treatment of MDS, particularly in high risk patients and goes some way to providing for the unmet need outlined above. In two randomised trials azacitidine has shown an overall survival advantage for treated patients. The first randomised trial carried out in the USA was hampered by a crossover from the supportive care arm to the active azacitidine arm (Lewis R Silverman et al. Randomised controlled trial of azacitidine in patients with the myelodysplastic syndrome: A study of the Cancer and Leukaemia Group B. JCO 20; 10, 2002: 2429-2440). However, a landmark analysis at 6 months showed an additional survival advantage for all patients randomised to azacitidine or crossing over to azacitidine within 6 months of randomisation compared to those who never crossed over or crossed beyond 6 months. In the second international, multicentre randomised trial (Fenaux P et al for the international Vidaza high-risk MDS survival study group. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncology 2009; 10: 223-232) patients with MDS, AML or chronic myelomonocytic leukaemia (CMML) and with 10-30% blasts (358 patents) were randomised 1:1 to azacitidine or conventional care regimens selected by each site. Azacitidine showed better overall survival than the combined cohorts of patients treated with conventional care regimens, either low dose cytosine arabinoside, supportive care or intensive chemotherapy (24.5 months V 15 months) and was better than the individual cohorts of supportive care or low dose cytosine arabinoside. At 2 years, by Kaplan-Meier estimates, 50.8% of azacitidine treated patients were alive compared with 26.2% in the conventional care group. The time to transformation to AML was also longer for azacitidine (17.8 months) compared to the supportive care group (11.5 months). In some patients the hypomethylating action of
Azacitidine may improve blood counts and survival without necessarily reducing blast counts and may lead to a revision of the way we assess response in these patients.

There may be a sub group of high risk patients with abnormalities of chromosomes 7 and/or 5 who have a particularly good response to hypomethylating agents. This group of patients with MDS or AML have traditionally had a dismal prognosis with a high rate of chemotherapy resistance and fewer than 10% of patients surviving for 2 years. In a joint report including 31 patients from Kings College Hospital in the UK and MD Anderson Cancer Centre in the USA there was a response rate of 50% for patients with an isolated chromosome 7 abnormality and 36% for patients with complex cytogenetics including chromosome 7 abnormalities. The overall survival was significantly longer for patients responding to azacitidine compared to those not responding. The MD Anderson has recently updated their experience at the 2008 American Society of Hematology on patients treated with azacitidine or the related hypomethylating agent decitabine. The complete response rate in 81 patients with AML or high risk MDS and a chromosome 7 or a chromosome 5 abnormality was 41%. Comparison to a cohort of 151 patients treated with conventional chemotherapy over the same time period suggested a superior overall survival for the azacitidine or decitabine treated group (median duration of CR 45 weeks v 23 weeks). In the recently published phase III randomised trial (Fenaux et al, 2009) this subgroup of chromosome 7 involved patients was analysed. The median survival for patients with -7/del(7q) treated with azacitidine was 13.1 months compared to 4.6 moths for patients in the combined conventional care arms. Whilst these data are on relatively small numbers of patients there appears to be a consistent message in the literature that patients with poor prognostic cytogenetic abnormalities benefit from azacitidine and this is an important observation that needs to be studied further.

At present few patients outside major centres with a research interest in MDS would receive active treatment other than supportive care and perhaps low dose chemotherapy. This partly relates to the frailty of this elderly patient population but also significantly to the 'professional nihilism' that prevails amongst treating physicians for the usefulness of the presently available treatments. The availability of a well tolerated, effective and outpatient based therapy like azacitidine is crucial to reversing this negative approach to this patient cohort. Azacitidine is available in the USA for all WHO subclasses of MDS. The European license will apply the therapy to the cohort of patients defined in the second randomised trial, namely patients with MDS, CMML and AML and with 10-30% blast cells. This group of high risk patients currently has a poor prognosis with a median survival of ~4-12 months according to the IPSS working group data base and as outlined above there are presently no available effective therapies for the vast majority of patients who are not allograft candidates. I strongly believe that azacitidine should be available as first line therapy within the UK for MDS patients with Int-2 and High IPSS scores and CMML and AML patients with less than 30% blasts and become the current standard of care for these patients.

The treatment would be given in all haematology units where BCSH level 2-4 care is delivered. This would be in haematology day care units but in time might be deliverable by trained community nurses with close haematology outpatient supervision. The treatment and its support are well within the scope of units treating malignancy with bone marrow suppressive chemotherapy and no additional infrastructure would be required, though there are pharmacy issues as outlined in later sections.
The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient’s quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Azacitidine is given as a subcutaneous injection in the outpatient setting. The license therapy is 75mg/m^2 for 7 days in every 28. The main concern is the short stability of the preparation and hence the need to make the injection up in sterile pharmacy units on a daily basis including Saturday and Sunday. This clearly has resource implications for chemotherapy pharmacies and has proven problematic in trial participation from within the UK. Some alternative dosing options have been considered so as to avoid weekend dosing. A recently published open-label study randomly assigned patients to one of three dose schedules: giving the licensed dose (75mg/m^2) 5 days out of 28 (5 schedule), giving a reduced dose (50mg/m^2) for 5 days, missing the weekend out and then giving a further 5 days (5-2-5 schedule) out of 28 and thirdly giving the licensed dose (75mg/m^2) drug Monday-Friday, missing the weekend and giving the final two doses on the following Monday and Tuesday (5-2-2 schedule) out of 28. Reassuringly, all three regimens produced similar haematological improvement, red blood cell transfusion independence and safety responses to those described for the licensed 7 straight day injections. However, this is an ongoing issue with regards to implementing the licensed therapy.

The treatment compares favourably with intensive chemotherapy and is perhaps similar to delivering low dose chemotherapy in the outpatient setting. The major side effect is bone marrow suppression. Within the French ATU compassionate use programme in 90 patients, which perhaps reflects widespread community experience more so than a randomised trial, grade 3-4 cytopenias led to dose reductions in 17% of patients and hospitalisation in 13% of patients with no treatment related deaths. Overall, Grade 3-4 granulocytopenias of 50-60% and thrombocytopenias of 50% are described in the literature leading to infection in about 20% of patients. The management of grade 3 and 4 bone marrow failure including transfusion support with red cells and platelets and treatment of neutropenic sepsis is standard practice for

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Professional organisation statement template
Azacitidine for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukaemia, and acute myeloid leukaemia
haematology units providing BCSH level 2-4 care. Some patients suffer grade 1-2 nausea and about one third of patients get a subcutaneous injection site reaction which is readily managed with topical NSAID and oral paracetamol.

The maximum number of treatment cycles is contentious. Within the published data most responses are assessed after a minimum of 4 cycles of treatment, with a large range of total numbers of cycles of treatment delivered (1-28). However, there are clearly patients who demonstrate response beyond 4 cycles. In the Silverman randomised trial response was assessed after 4 cycles and those in CR received a further 3 cycles whilst those in PR remained on treatment until documented CR or progression. Within the second randomised trial (Fenaux et al, 2009) the median number of cycles delivered was 9 (4-15) with a trial target number of 6. The survival curves separated after 3 months which equates to about 3 cycles of azacitidine. The optimal number of cycles is unclear. Silverman has recently reported at the American Society of Haematology in 2008 that response clearly relates to the number of treatment cycles given. The maximum response can take up to 11 additional cycles beyond initial response with a median number of 8 additional cycles of treatment required for maximal response. There are limited data on long term maintenance therapy. Perhaps a pragmatic approach is a minimum of 6 cycles and a maximum of two cycles beyond CR or maximum haematological improvement (HI)? The primary endpoint in the randomised trials was overall survival which is entirely appropriate for this cohort of patients with a short median survival. In the Silverman randomised trial the authors felt that a modified endpoint of time to death or transformation to AML was the most meaningful clinical end point, because survival and quality of life decline rapidly for patients with MDS after AML develops. Traditionally, response in high risk MDS and AML patients has been judged predominantly in terms of achieving complete remission (CR) - a state of near normal blood counts and a reduction in bone marrow blasts to < 5%. In the context of azacitidine therapy complete remissions are more frequent than low dose cytarabine, however, a survival advantage is seen without necessarily receiving CR. Improvement in cytopenias (HI) and reduction in transfusion requirement on a monthly basis may, therefore, be better tools for assessing patients’ response to treatment than bone marrow blast cell count.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that
have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

As outlined above, the implementation of the technology is well within the current therapeutic scope of all BCSH level 2-4 centres in the UK. The overwhelming issue to be clarified is the practical dosing issue with regards to weekend pharmacy provision.