**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE**

**Health Technology Appraisal**

**Appeal Hearing**

# Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia

## Decision of the Panel

## Introduction

1. An Appeal Panel was convened on 1st June 2010 to consider an appeal against the Institute's Final Appraisal Determination, to the NHS, on the use of azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia.

2. The Panel comprised Professor Sir Michael Rawlins (Chair of the Panel and Chair of NICE), Mr Jonathan Tross (Non-executive director of NICE), Mr Robert Osborne (Lay representative), Professor Peter Stonier (Industry representative), and Professor Robin Ferner (NHS representative).

3. The Royal College of Physicians was one of the appellants, and Professors Rawlins, Stonier, and Ferner declared that they were Fellows of the College. No other conflicts of interest were declared by members of the Panel.

4. The Panel considered appeals submitted by Celgene Ltd; jointly by The MDS UK Patient Support Group (MDS UK), The Leukaemia Society, and the Rarer Cancers Society; jointly by The Royal College of Pathologists and the British Society for Haematology; and jointly by the Royal College of Physicians, the National Cancer Research Institute Haematological Oncology Clinical Studies Group, the Royal College of Radiologists, the Association of Clinical Pathologists, and the Joint Collegiate Council for Oncology.

5. In addition, the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel: Professor Ken Stein (Vice-chair of the Appraisal Committee), Dr Elisabeth George (Associate Director, Centre for Health Technology Evaluation), Ms Whitney Miller, Dr Meindert Boysen (Programme Director, Centre for Health Technology Evaluation), Professor John Cairns (member of the Appraisal Committee), and Mr Bhash Naidoo.

6. The Institute's legal advisor (Mr Stephen Hocking, Beachcroft LLP) was also present.

7. Under the Institute's appeal procedures members of the public are admitted to appeal hearings and several members of the public were present at this appeal.

8. There are three Grounds on which an appeal can be lodged:

(a) The Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process;

(b) The Institute has prepared guidance that is perverse in light of the evidence submitted;

(c) The Institute has exceeded its legal powers.

9. The Chair of the Appeal Committee (Dr Maggie Helliwell), in preliminary correspondence, had confirmed that the appellants had potentially valid grounds of appeal as follows:

(a) Celgene Ltd: Grounds 1, 2, and 3

(b) MDS UK and co-appellants: Grounds 1, 2, and 3

(c) Royal College of Pathologists and co-appellant: Ground 2

(d) Royal College of Physicians and co-appellants: Ground 2

10. Azacitidine is an anticancer agent given by subcutaneous injection for the treatment of myelodysplastic syndromes of higher severity and for the treatment of certain leukaemias.

**Appeal by Celgene Ltd**

**Ground 1––The Institute has failed to act fairly and in accordance with the appraisal procedures set out in the Institute's Guide to the Technology Appraisal Process**

**Celgene 1.1 The Appraisal Committee was obliged to appraise products in accordance with the Final Scope, which listed chemotherapy as a comparator; ignoring chemotherapy was against the Institute's Guide to the Technology Appraisal Process**

11. Ms Jemima Stratford, QC, for Celgene, argued that the Appraisal Committee had failed to act fairly and in accordance with published procedures by comparing azacitidine with best supportive care only, and excluding chemotherapy as a comparator. This departure from the agreed Scope represented an 'informal re-scoping' that was not a part of the established procedure.

12. Professor Stein, for the Appraisal Committee, explained that the Committee had considered that they should take best supportive care as the comparator after having examined both low-dose and standard-dose chemotherapy groups in the key AZA-001 clinical trial. The Committee had tried to identify those characteristics that determined which group a patient would be allocated to, but had been unable to do so. There was, moreover, a wide range of clinical practice in the management of MDS, in the UK, with some haematologists using only best supportive care.

13. However, Professor Stein accepted that AZA-001 was a trial in which patient preference helped to determine allocation to treatment, and that this was an uncommon clinical trial design. In addition, the Appraisal Committee had learnt from the Expert Review Group that the incremental cost-effectiveness ratio for the entire group of patients treated in AZA-001 was estimated to be around £60 000 per quality-adjusted life year.

14. The Appeal Panel accepted that the Appraisal Committee had considered chemotherapy as a comparator against which to judge azacitidine during the appraisal. It had not, ultimately, based its recommendations on that consideration, but that could not properly be characterised as an informal re-scoping. It had not, therefore, departed from the Institute's procedures for Technology Assessment.

15. The Appeal Panel therefore dismissed the appeal on this point.

**Celgene Appeal under Ground Two**

**Ground 2––The Institute's Final Appraisal Determination is perverse in the light of the evidence submitted**

**Celgene 2.1 Omitting chemotherapy as a comparator was perverse, since it is in widespread use**

16. Ms Stratford put forward the view that the Appraisal Committee was perverse in ignoring chemotherapy, which was widely used in clinical practice. The Appraisal Committee had accepted, in paragraph 4.2 of the Final Appraisal Determination, that the treatments in AZA-001 trial were 'broadly representative' of practice in the United Kingdom. In that trial, 41% were allocated to low-dose or standard-dose (intensive) chemotherapy groups. The Company had, in addition, provided data from a survey of leading haematologists, showing that chemotherapy was commonly used. The Appraisal Committee took note of the survey, to the extent that they interpreted it to show that practice varied from centre to centre.

17. The Appraisal Committee appeared to Celgene to have misinterpreted some of the evidence presented. It was true that, as stated in paragraph 4.2 of the Final Appraisal Determination, patients who have stem cell transplants receive prior chemotherapy. But it was not true that such patients represent the majority of those who receive chemotherapy.

18. Professor Ghulam Mufti, for MDS UK and co-appellants, explained the AZA-001 trial, involved patients with higher-grade myelodysplastic syndromes from 79 centres in 15 countries. Conventional treatment varied but could be

one of three regimens: best supportive care, low-dose chemotherapy, or standard-dose (intensive) chemotherapy.

19. He explained that patients fulfilling the entry criteria for the AZA-001 trial discussed with their physician which of the three approaches to treatment might be best for them, and the physician and patient decided which treatment group the patient would prefer. Once this was decided, patients within groups were randomized to have either their chosen regimen or azacitidine.

20. Dr Dominic Culligan, for the Royal College of Pathologists and the British Society for Haematology, stated that the sole evidence for the efficacy of azacitidine that was before the Appraisal Committee was the AZA-001 trial, in which 41% of patients were in one or other of the chemotherapy groups. This was a very significant proportion. Chemotherapy should have been considered as a comparator.

21. Professor David Bowen, for the Royal College of Physicians and co-appellants, emphasized that, while the majority of patients with higher-grade myelodysplastic syndrome in the United Kingdom received best supportive care, the proportion who received chemotherapy of one sort or another was not negligible, and chemotherapy should therefore have been included as a comparator.

22. Professor Bowen accepted that the Appraisal Committee had discussed comparators, but the Final Appraisal Determination failed to make clear why it had reached the decision to use only best supportive care in drawing conclusions about cost effectiveness.

23. Professor Stein stated that the question of comparators was very difficult. He could not recall that the matter of patient preference, which had been one of the factors determining allocation to treatment group in the AZA-001 trial, had been discussed by the Appraisal Committee. He accepted, however, that patient preference trials need to be considered rather differently

from other trials. He added that the Committee had felt unable to produce advice based on chemotherapy as a comparator, because of the difficulty in identifying *a priori* which patients would receive chemotherapy. There did not appear to be a defined cohort for whom particular recommendations could be made.

24. Professor Cairns, for the Appraisal Committee, emphasized that the Committee had considered chemotherapy as a comparator, but had decided that best supportive care was the relevant comparator when drafting guidance.

25. The Appeal Panel considered whether it had been reasonable to ignore chemotherapy as a basis for recommendations, given the evidence that some patients, in discussion with their physicians, wished to receive chemotherapeutic treatment. There appeared to be two issues in play: the extent to which chemotherapy was in use; and whether it was possible to base guidance on chemotherapy as a comparator.

26. Although the evidence was not comprehensive, and very considerable variation in practice was revealed, the Panel concluded that on the evidence before it the Committee could not reasonably conclude that chemotherapy was not in routine use within the NHS. While the extent of that use was unclear, and this may be a highly relevant issue, there was no reason to discard chemotherapy altogether as the basis for recommendations on this ground.

27. The remaining issue was whether it was reasonable to reject chemotherapy as a basis for recommendations, given the problem of identifying *a priori* the group of patients who would have received chemotherapy. The Panel was conscious of those problems, but observed that the same point applied to using best supportive care as a comparator. The Panel did not understand why the Committee had adopted best supportive care as the sole basis of comparison, as opposed to working with a ‘blended’ incremental cost-effectiveness ratio (that is, combining the results of

best supportive care and low-dose chemotherapy) or indeed adopting low-dose chemotherapy, alone, as the comparator. Any or all of these might be reasonable approaches.

28. Furthermore, the Panel would have required more evidence before being persuaded that the problems of providing workable guidance based on both BSC and chemotherapy were truly insuperable. In the absence of a satisfactory explanation on these points the Panel has no option but to find that it was not reasonable to discard low-dose chemotherapy as a comparator.

29. The Appeal Panel therefore upheld the appeal on this point.

30. The Appeal Panel requests that the Appraisal Committee reappraise azacitidine, ensuring that the comparators take into account both best supportive care and low-dose chemotherapy. If after reconsideration the Committee still considers that only best supportive care should form the basis of its recommendations, it should provide clear and detailed reasons for doing so.

**Celgene 2.2.1 The Committee has not taken account of the significant life extension attributable to azacitidine, when the 9.5 months' extension is well above the extensions previously accepted as meeting End-of-Life criteria**

31. Ms Stratford maintained that, while paragraph 4.12 of the Final Appraisal Determination made it clear that the Appraisal Committee had considered that azacitidine fell within the end-of-life criteria, it failed to take sufficient account of the very substantial increase in life-expectancy, being a median of 9½ months of high-quality extra life. Paragraph 4.9 stated that the economic analysis may have underestimated the gain in quality of life from azacitidine but that the impact was likely to be small. In fact the sensitivity analysis suggested that the underestimate might reduce the cost per quality-adjusted life year by as much as £10 000.

32. The Panel was told by Professor Stein that the Appraisal Committee had been impressed by the very considerable gain in life. The data were robust, and the results were believable. However, the cost was very high.

33. Dr Carl Gibbons, for Celgene Ltd, accepted that the incremental cost-effectiveness ratio captured both the time by which life was extended and the improvement in quality of life. However, for treatments at the end of life, the Committee had the discretion to decide by how much to multiply the normal threshold of acceptability.

34. Dr Gibbons accepted that, in using a multiplier, benefits were counted twice.

35. Professor Stein explained that the Appraisal Committee had to consider what multiplier might appropriately be applied to the usually accepted limits on the incremental cost-effectiveness ratio to allow for the end-of-life element. It had done so, and reached the conclusion that a multiplier of 2.1 would be needed to bring the incremental cost-effectiveness ratio within an acceptable range. That multiplier was too high for the Committee to recommend the use of this treatment to the NHS. Dr Boysen added that even the multiplier of 2.1 assumed as its starting point a cost per quality-adjusted life year of £30 000; this was itself above the figure where recommendation could normally be regarded as automatic (£20 000).

36. The Appeal Panel considered whether the Appraisal Committee had acted reasonably in using its judgment to decide what represented an acceptable multiplier. It understood that the incremental cost-effectiveness ratio fully counted the gain in life expectancy once, and the argument was in effect that there was something additional in a life expectancy of this magnitude. The Panel agreed that the Committee had not been unreasonable in concluding that a multiplier of 2.1 was too high to recommend.

37. The Appeal Panel therefore dismissed the appeal on this point.

**Celgene 2.2.2 It was perverse to criticise azacitidine, in terms of the End-of-Life policy, for not having 'robust' data to support use**

38. Ms Stratford described this as a 'defensive' point, and advanced no additional arguments to support it at the hearing. The Appeal Panel noted that paragraph 4.3 of the Final Appraisal Determination stated that 'the estimates of total overall survival appeared robust' and that paragraph 4.12 stated that 'the best available estimates of the incremental cost-effectiveness ratio were sufficiently robust to conclude that azacitidine meets the criteria for being a life-extending, end-of-life treatment.'

39. The Appeal Panel dismissed the appeal on this point.

40. The Appeal Panel asked that, in considering the matters dealt with elsewhere in this decision, the Appraisal Committee should consider again the robustness of the evidence presented to it, including the evidence on quality of life.

**Celgene 2.3 It is perverse to appraise an ultra-orphan drug using the same methods as are used to appraise 'ordinary' drugs**

41. Ms Stratford expressed the view that azacitidine, used to treat higher-grade myelodysplastic syndromes, was applicable to only 700 patients a year in the United Kingdom, and therefore, according to a document on the NICE website, should be classified as an 'ultra-orphan' drug, and should have been appraised by the Committee with that in mind. NICE had itself accepted that simply applying its normal processes to such drugs would never produce a positive recommendation.

42. Professor Sir Michael Rawlins explained that the document referred to was a written response by the Institute to an enquiry from the Department of Health, made some years ago. It was not, and had not been intended to be, guidance of any sort. Nor had the document ever been provided to the Appraisal Committee as additional advice. The Institute had placed the document on the NICE website after it had been made public by the

Department of Health as a consequence of a request under the Freedom of Information Act. The Department of Health had not, in fact, acted on the advice.

43. In any event, Sir Michael continued, azacitidine would not have been considered an ‘ultra-orphan’ drug since it was being considered for a wide variety of indications, not one extremely rare indication.

44. Further, the document predated the End-of-Life policy, which did allow for a more flexible approach to some drugs in use in small patient populations (including this one). The argument that azacitidine could never be recommended if appraised according to usual processes was not borne out by some of the incremental cost-effectiveness ratios in this case, bearing in mind Professor Stein's comments about the cost of the drug, which was a matter within Celgene's control.

45. The Appeal Panel considered that there was no case for the Appraisal Committee to have considered the use of azacitidine in a manner different from the approach described in the Institute’s Guide to the Technology Appraisal Process.

46. The Appeal Panel therefore dismissed the appeal on this point.

## Celgene appeal under Ground 3

### Ground 3 The Institute has exceeded its legal powers

### Celgene 3.1 It was wrong of the Appraisal Committee to depart from the Final Scope

47. Ms Stratford argued that, if Celgene’s appeal point under Ground 1.1 was upheld, then it followed that the Institute had exceeded its legal powers. In the event, the Appeal Panel had dismissed the appeal point 1.1.

48. The Appeal Panel therefore dismissed the appeal on this point.

### Celgene 3.3 The Guidance contravened the Human Rights Act

49. Both Celgene and the MDS UK Patient Support Group argued that the guidance contravened NICE's duties under the Human Rights Act. Specifically, they argued that the failure to recommend a life-extending treatment such as azacitidine contravened Articles 2, 3 and 8 of the European Convention on Human Rights, as well as amounting to discrimination in the enjoyment of those rights contrary to Article 14.

50. The Panel had before it a written note of legal advice from its legal advisor, as well as written responses to that advice from Celgene, MDS UK, and the Appraisal Committee. It took all of these comments into account, as well as oral observations made by Ms Jemima Stratford, QC, on behalf of Celgene.

51. It is convenient to take the arguments under Article 2 and Article 3 together. The contention is that by not recommending a treatment that is life-extending, the guidance subjects patients to inhuman or degrading treatment contrary to Article 3, or fails to ensure their lives are protected contrary to Article 2, or both.

52. The Panel did not accept these arguments. The suffering of the patients is unquestioned, but it is caused by their illness, not by the guidance. The Panel understood that both Articles 2 and 3 impose certain positive obligations, and it accepted that where a treatment is generally available either of these articles may require it to be provided to an individual patient, but it did not accept that the articles extended to an obligation to recommend a treatment within a national health service in the first place.

53. Further, the Panel was not persuaded that the guidance does increase suffering in a way attributable to the State, in the way that deportation increased suffering in the *D v UK* case cited by Celgene. Actively moving a patient from a situation where treatment is (and will continue to be) provided, to one where treatment is not provided, seems to be an act of a different

quality to not recommending treatment for all patients at the outset. First, D was treated differently from fellow patients, whereas here all patients are treated alike. Secondly, in D there was a positive act, whereas here there is a failure to act. Thirdly, D had treatment terminated, whereas here treatment is not initiated. (The guidance correctly allows patients who are currently being treated to continue receiving treatment.)

54. Fundamentally, despite Celgene's correct observation that each case must be considered on its facts, the argument under Articles 2 and 3 proved too much. Neither Article 2 nor Article 3 confers qualified rights. If failure to fund a treatment engages either right, then it is hard to see how Celgene's acknowledgement that there are limits to public resources could ever be relied on in practice. That each case depends on its facts is an insufficient answer, because different cases must still be dealt with consistently and in the light of the same underlying principles. Even allowing that not every condition is so serious, and not every treatment so beneficial, as to engage either Article, very many conditions and treatments would engage these rights, and the ability of any signatory state to manage its public healthcare budget would seem to be gravely undermined if the appellant's arguments were correct. Not only would this be impractical, it would seem to remove an essentially political or policy decision about the priorities for public spending into the judicial arena, which seems incorrect in principle. No case decided to date seems to imply that this is the law.

55. Turning to Article 8, the Panel did not accept the advice of its legal advisor that Article 8(1) was breached at all. The Panel did not agree with the Committee that ‘respect’ under Article 8 limits the scope of Article 8 to essentially procedural issues around how the state interacts with the citizen. Elements of Article 8(2) do deal with such issues but Article 8 is a substantive right and may be infringed even if the State has acted carefully and ‘respectfully’. However the Panel did prefer the argument on behalf of the Committee, that while some decided cases showed that Article 8(1) may be engaged by access to medical care (although the cases are not entirely

consistent even on that point), the cases set the threshold for a breach of Article 8(1) very high. The Panel did not accept that that threshold was reached on the facts of this case.

56. In the light of that conclusion it was not necessary for the Panel to consider in detail whether the guidance was in accordance with law and necessary for one of the permitted purposes listed in Article 8(2).

57. It follows that the Panel did nevertheless accept that, contrary to the argument of the Committee, the question of access to this treatment is within the ambit of Article 8, and therefore it agreed with the appellants that Article 14 was engaged. It also accepted that most patients with myelodysplastic syndromes are elderly, and that while a small percentage of younger patients may be eligible for allogeneic stem cell transplantation, for older patients who could not receive a transplant, azacitidine would be the most clinically effective treatment.

58. Nevertheless the Panel did not accept that Article 14 was breached. It considered that the putative right in play here is the right to access azacitidine, not the right to access treatment for myelodysplastic syndromes, still less to have a particular outcome from treatment. All patients are treated equally in that regard. It did not agree that this is a case of indirect discrimination, as there is no difference in treatment or outcome at all on the question of access to azacitidine.

59. If, contrary to that conclusion, the issue is access to treatment generally for myelodysplastic syndromes, then the Panel accepts that younger patients have access to a treatment option not available to older patients (that is, bone marrow transplantation). This would still be the case even azacitidine were to be recommended. It is common ground that for patients eligible for transplantation, this would usually be the preferred treatment option; in other words, older patients would still receive a different treatment and would still be

at a disadvantage in outcome. This is a consequence of age, of the disease, and of the relative merits and rigours of transplantation and azacitidine, and not reflective of any act of discrimination.

60. Assuming, contrary to its finding, that not recommending azacitidine is discriminatory because transplantation is available to younger patients, the Panel would have found that such discrimination was justified. The guidance seeks to achieve the legitimate objective of securing cost-effective use of NHS resources, and the Panel considers it a proportionate way to achieve that objective, having regard to the transparency of the appraisal process, the fact that this did not appear to be a borderline case (as currently appraised, in any event), and the observation above that differences in outcome would persist even if azacitidine had been recommended.

**61.** The Appeal Panel therefore dismissed the appeal on this point.

**MDS UK and co-appellants appeal under Ground 1**

**Ground 1––The Institute has failed to act fairly and in accordance with the appraisal procedures set out in the Institute's Guide to the Technology Appraisal Process**

**MDS UK 1.1 Quality of Life evidence was offered but was ignored**

62. Professor Rodney Taylor, for MDS UK, explained that he was a gastroenterologist who had suffered from myelodysplastic syndrome. The utilities used in the submission on azacitidine had been based on a cohort of patients with oesophageal cancer. This was a very different condition from myelodysplastic syndrome, and the Appraisal Committee had indicated in paragraph 4.9 of the Final Appraisal Determination that the Company's estimates of the utility gain from azacitidine might be an underestimate.

63. However, when MDS UK had offered the Committee data on the utility gain of azacitidine in patients with myelodysplastic syndromes, the Committee had not accepted the offer. MDS UK had been constrained by space in its

original application. It had not included numerical values in its response to the Appraisal Consultation Document.

64. Professor Stein stated that the Appraisal Committee had before it a great deal of information, and had not taken up the offer from MDS UK. The Committee expected the data to outline how blood transfusions and fatigue substantially diminished the quality of life, which expert patients had already explained. Utility estimates would have been helpful, but the Appraisal Committee was not aware that the data contained these.

65. Dr Meindert Boysen, for the Appraisal Committee, explained that when comments on the Appraisal Consultation Document were received, the Committee had to balance the value of information that might change the Appraisal Committee's recommendation against the danger of prolonging the process of appraisal when new information is presented.

66. Professor Stein agreed that MDS UK had received no response from the Committee to its offer, and that in general the Committee did not respond directly to consultees.

67. Mr Brian Kelly, legal advisor to MDS UK, accepted that the Committee's views were contained in the response to comments on the Appraisal Consultation Document, and indicated that the Committee considered that the information would have only a minimal effect on the results.

68. The Appeal Panel considered whether the Appraisal Committee was obliged by the Institute's procedures to examine all evidence offered to it as comment on the Appraisal Consultation Document but not provided. It decided that there was no such obligation.

69. The Appeal Panel therefore dismissed the appeal on that point.

70. However, the Appeal Panel considered that it would have been desirable for the Appraisal Committee to examine the quality of life data, available to MDS UK, to decide whether they could help materially in establishing better estimates of utilities during treatment for myelodysplastic syndromes, and it might have helped if MDS UK had pro-actively provided it. It requested that these data would be provided by MDS UK for consideration during the Committee's further appraisal of azacitidine.

**MSD UK Ground 1.2 There was a failure to consult in an open and transparent manner**

71. Professor Taylor described how, at the Appraisal Committee's meeting on 7th January 2010, the Chair of the Committee stated that he had asked a haematologist colleague whether he used chemotherapy for patients with high-risk myelodysplastic syndromes, and the colleague had said that he did not. The Appraisal Committee already had before it the details of the AZA-001 study; the views of its own clinical experts; and the data from Celgene's survey. The addition by the Chair of the personal opinion of another haematologist was procedurally unfair.

72. Professor Stein confirmed that he had asked a haematologist in his own Trust, who had said that he did not use chemotherapy, and he had advised the Committee of this. He added that he understood that all Committee members were expected to use their own knowledge and expertise in reaching their decisions, and that he had done no more than find out what the practice was in his Trust.

73. The Appeal Panel understood and shared the appellants' concerns. Professor Stein was right that Committee members were expected to draw on their background knowledge and expertise, and that it would be reasonable to use that background knowledge to test the credibility of the evidence being presented for consideration, provided they properly appreciate its limitations. What is not reasonable, or fair, is for new evidence to be introduced otherwise than in accordance with the published procedures.

74. With some concern, the Panel concluded that what Professor Stein had done was to test the evidence in the light of his background knowledge, rather than to introduce new evidence. In this case, as it happened, the information only re-inforced what was already clear from the other information before it: that there was no agreed management for higher grade myelodysplastic syndromes, and that different clinicians treated them differently.

75. The Appeal Panel therefore dismissed the appeal on this point. However, the Panel found it understandable that the appellants should be concerned, and Professor Stein had undoubtedly put himself in a position where his actions could be misunderstood. It would be better if that was avoided in future.

**MDS UK and co-appellants appeal under Ground 2**

**Ground 2––The Institute's Final Appraisal Determination is perverse in the light of the evidence submitted**

**MDS UK 2.1 The Institute's recommendation is perverse as the Appraisal Committee ignored key evidence on the quality of life**

76. The Appeal Panel had explored this point under Ground 1. The Panel had accepted that the Committee was not obliged to consider the information offered. Nor was it unreasonable to exclude it from consideration.

77. The Appeal Panel therefore dismissed the appeal on this point.

78. However, as already indicated above, the Appeal Panel considered it to have been desirable for the Appraisal Committee to examine the data to decide whether they helped materially in establishing better estimates of utilities during treatment for myelodysplastic syndromes, and expressed the hope that these data would be provided for further consideration during further appraisal of azacitidine.

**MDS UK 2.2 Misunderstanding of myelodysplastic syndromes led to a perverse reliance on best supportive care as the only comparator**

79. The Appeal Panel had considered this matter under Celgene's appeal point 2.1.

80. The Appeal Panel upheld the appeal on this point.

**MDS UK 2.3 The recommendation is perverse given the 9½ months' extension to life**

81. Professor Taylor reiterated that azacitidine represented a true end-of-life treatment that extended life substantially more than other end-of-life treatments that the Institute had considered. The quality of life was also greatly enhanced by a reduced need for, or a freedom from, transfusions of blood products, and by reduced fatigue.

82. Professor Stein confirmed that the Appraisal Committee had found the data on the effectiveness of azacitidine robust, and had been impressed by the extension to life that this treatment offered. However, the calculated gain in quality-adjusted life years fully took account both of the estimates of extension to life and of the improved quality of life. Even allowing for this, and for the uncertainty in the estimates, the incremental cost-effectiveness ratio for azacitidine was unacceptably high as it stood.

83. As discussed above, Professor Stein explained that a multiplier of 2.1 would have been needed to bring the incremental cost-effectiveness ratio within an acceptable range, and that multiplier was too high for the Committee to recommend the use of this treatment.

84. The Appeal Panel discussed whether the approach by the Committee had been reasonable. There were uncertainties in the relevant estimates, and these had been taken into account in calculating the incremental cost-effectiveness ratio, which fully covered both the extension to life and the improvement in quality of life. It was for the Appraisal Committee to determine what multiplier might be appropriate, and it had done so reasonably.

85. The Appeal Panel therefore dismissed the appeal on this point.

**MDS UK and co-appellants appeal under Ground 3**

**Ground 3 The Institute has exceeded its legal powers**

86. MDS UK raised essentially the same issues in connection with the Human Rights Act as were raised by Celgene, and for the reasons given above, the Appeal Panel rejected the appeal on those grounds.

87. MDS UK also alleged that the guidance was unlawful in that it would require clinicians to act unethically, in that clinicians are obliged to show respect for human life, and to act in their patients' best interests, and that prolonging life will usually be in the best interests of the patient.

88. The Appeal Panel observed that a clinician's ethical duties only have effect within the context of the resources and treatments available to him or her. They are not determinative of the question of what resources should be made available by the NHS, not least because the NHS as an organisation is not subject to those same duties. The relevant duty might instead be found in s.1 of the National Health Service Act 2006 which reads

> *The Secretary of State must continue the promotion in England of a comprehensive health service designed to secure improvement—*
>
> *(a) in the physical and mental health of the people of England, and*
>
> *(b) in the prevention, diagnosis and treatment of illness*

89. The Panel was satisfied that this guidance did not contravene that duty, nor any right contained in the NHS Constitution.

90. It therefore rejected the appeal on this Ground.

**Royal College of Pathologists and British Society for Haematology**

**Ground 2––The Institute's Final Appraisal Determination is perverse in the light of the evidence submitted**

**Royal College of Pathologists and British Society for Haematology 2.1 It was perverse to use only best supportive care as a comparator**

91. This matter had been discussed under point 2.1 of Celgene's appeal, which the Appeal Panel had upheld.

92. The Appeal Panel therefore upheld the appeal by the Royal College of Pathologists and British Society for Haematology on this point.

**Royal College of Physicians and co-appellants**

**Ground 2––The Institute's Final Appraisal Determination is perverse in the light of the evidence submitted**

**Royal College of Physicians and co-appellants 2.1 It was perverse to use only best supportive care as a comparator**

93. This matter had been discussed under point 2.1 of Celgene's appeal, which the Appeal Panel had upheld.

94. The Appeal Panel therefore upheld the appeal by the Royal College of Physicians and co-appellants on this point.

**Conclusion**

95. The Appeal Panel upheld the Appeals under Ground 2 on the following points:

a) Celgene point 2.1

b) MDS UK and co-appellants point 2.2

c) Royal College of Pathologists and British Society for Haematology point 2.1

d) Royal College of Physicians and co-appellants point 2.1

96. The Appeal Panel dismissed appeals on all other points.

97. The Appeal Panel requests the Appraisal Committee to reconsider the guidance issued, taking account of both best supportive care and low-dose chemotherapy as comparators. The Appeal Panel also requests the Appraisal

Committee to examine the data on quality of life, and consider the utilities available to it from MDS UK.

98. There is no possibility of further appeal within the Institute against this decision of the Appeal Panel. However, the decision of the Appeal Panel may be challenged by an interested party through an application to the High Court for permission to apply for judicial review. Any such application must be made promptly and in any event within three months of this Decision or the issuing of the Guidance.