Decision Support Unit Project Specification Form	
Project Number	
Appraisal title	Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia, and acute myeloid leukaemia
Synopsis of the technical issue	**1. Final Appraisal Determination** In March 2010, a Final Appraisal Determination (FAD) for the above appraisal was issued, in which azacitidine was not recommended. This decision was based on an ICER of approximately £63,000 per QALY gained compared with best-supportive care. However, in the pivotal trial, 3 conventional care regimens were used as pre-randomisation subgroups: best supportive care alone, low-dose chemotherapy (plus best supportive care), and standard-dose chemotherapy (plus best supportive care). In this trial, azacitidine was compared with each of these conventional care regimens. The Committee based its decision on the comparison with best supportive care alone because firstly the majority of patients in the trial received best supportive care (≈60%), and secondly because the Committee received conflicting data on how patients would be selected for any of the above three conventional care regimens. These data showed pronounced variations in treatment patterns, which indicated that there is no nationally recognised standard of care for this patient population with regard to patients' eligibility for chemotherapy. The Committee also concluded that the manufacturer's model may have underestimated the gains in health-related quality of life resulting from treatment with azacitidine, but because the ICER estimate was largely driven by the incremental life years gained and was only minimally affected by the changes in health-related quality of life, the impact of underestimating the gains was likely to be small.

	2. Appeal of Final Appraisal Determination The FAD was appealed against , and the Appeal Panel upheld appeal Ground 2 points (as summarised below), and requested that the Appraisal Committee reconsider the guidance issued. *Upheld Appeal points under ground 2 – Use of best supportive care as the only comparator* The Appeal Panel considered two points: (1) the extent to which chemotherapy was in use; and (2) the extent to which it was possible to base guidance on chemotherapy as a comparator. The Panel concluded, on the evidence before it, that it did not consider it reasonable to discard low-dose chemotherapy (plus best supportive care) as a comparator. The Appeal Panel requested that the re-appraisal of azacitidine take into account both low-dose chemotherapy (plus best supportive care) and best supportive care alone as comparators. *Additional comments by the Appeal Panel* The MDS UK and co-appellants put forward the view that additional evidence on the quality of life of patients with MDS offered during consultation on the ACD should have been included. This point was dismissed by the Panel under Ground 1; however, it requested that these data be provided by MDS UK for consideration by the Committee during the requested re-consideration of the guidance. In the Appeal hearing it was also discussed that patient preference trials may need to be considered rather differently from other trials. **3. Post-Appeal Actions** In preparation for the re-consideration by the Appraisal Committee, the Institute has requested further information:

	From MDS UK: : a. a published study that provides health utility values in patients suffering from MDS, particularly on transfusion independence b. a published study on the common troublesome symptoms in MDS patients and the impact on quality of life, particularly regarding fatigue c. a published article describing the quality of life of MDS patients using data from the MDS Foundation's internet forums d. the questionnaires provided to patients that have taken part in the MDS Foundation's internet forums From Celgene: a. information on the interpretation of patient preference trials b. more comprehensive data on current clinical practice to explore the proportions of people receiving low-dose chemotherapy (plus best supportive care) and those receiving best supportive care alone c. clinical characteristics of people receiving low-dose chemotherapy (plus best supportive care) in routine clinical practice d. the inclusion of MDS UK's quality-of-life data in the most recent version (October 2009) version of the economic model; and e. Using the October 2009 economic model to establish ICERs using the updated quality-of-life data from MDS UK for (1) the entire population, and (2) for the respective

	groups eligible to receive low-dose chemotherapy (plus best supportive care), and best supportive care alone. This further information requires review by an academic group before being considered by the Committee.
Question(s) to be answered by DSU	1. Is there anything that the Committee has to consider differently from other trial results when it makes its judgement on the clinical effectiveness of a drug based on a patient /physician preference trial compared with other trial designs? 2. Does the data submitted by Celgene regarding current practice patterns and characteristics of patients receiving each of the comparative care regimens give a comprehensive view of UK clinical practice and allow a clear definition of subgroups? 3. Do the quality of life data from MDS UK remove uncertainty around the utility estimates and to what extent have the utility data provided by MDS UK been appropriately incorporated into the model?
How will the DSU address these questions	
How does this relate to the ERG?	These questions go beyond the work of the ERG because the further information (above) was not available during the appraisal.

Exact analyses required	1. An academic opinion on whether or not the fact that a trial was ‘patient/physician preference trial’ has a bearing on the interpretation of the trial results. The manufacturer has been similarly asked to comment; an academic opinion of the comment it submits is required. 2. A critical review of the data submitted by Celgene regarding current practice patterns and characteristics of patients receiving each of the comparative care regimens is required. 3. A critical review of the quality of life data submitted by MDS UK. 4. A critical review of the updated economic modelling (including the incorporation of the quality of life data from MDS UK) and report submitted by the manufacturer.