Has all the relevant evidence has been taken into account?

No. Section 4.4.5 of the ACD states that:

'the Committee was not provided with any observational data documenting survival times in people who received bevacizumab as a second or third-line treatment in clinical practice.'

This is factually inaccurate. Appendix 2 of our submissions contains details of observational data in which '*survival times in people who received bevacizumab as a second or third-line treatment in clinical practice'* were documented (i.e. the BRiTE registry and the ARIES registry).

This evidence has not been taken into account by the Committee. The results of BRiTE and ARIES are summarized briefly below (with further detail provided in our original submission).

BRiTE

In BRiTE the median survival beyond first progression for patients treated with bevacizumab + chemotherapy as a second line treatment was 19.2 months compared to 9.5 months for patients who received chemotherapy alone ($p<0.05$).

ARIES

The ARIES registry showed a trend towards superior overall survival for bevacizumab based second line therapy compared to chemotherapy alone (median OS for bevacizumab plus chemotherapy was 21.7 months, 95% CI 17.8-27.0 compared to 17.5 months, 95% CI 15.9-21.5 for chemotherapy alone).

Relevance of this evidence to the current decision problem

This data indicates that, in the real world, patients who receive bevacizumab in combination with chemotherapy after first line therapy appear to have longer progression-free and overall survival than those that are treated with chemotherapy alone (significantly so in the case of the BRiTE registry).

However as this data is not available limited to solely those patients who received non-oxaliplatin based chemotherapy and is not randomized (and so potentially subject to selection bias) it's relevance to the current decision problem is unclear.

Nevertheless, despite these limitations, observational data was submitted and has not been considered, or acknowledged, by the Committee.

Both BRiTE and ARIES are supportive of the findings of the randomized evidence available, and are aligned with the EMA's opinion that bevacizumab in combination with chemotherapy is efficacious and safe in the treatment of 2nd line mCRC.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Section 4.3.1. of the ACD states:

'The treatment cost for cetuximab plus FOLFIRI was estimated to exceed that for bevacizumab plus FOLFIRI by £5408, with costs for KRAS testing of £462, drugs costs of £3357 and administration costs of £1589. '

Given its current wording the following section of the sentence '*with costs for KRAS testing of £462, drugs costs of £3357 and administration costs of £1589*' may be misinterpreted.

These values were incremental rather than absolute costs yet currently it is plausible that these may be interpreted as being absolute.

We suggest the wording should be amended to reflect this. Perhaps "*The treatment cost for cetuximab plus FOLFIRI was estimated to exceed that for bevacizumab plus FOLFIRI by £5408, with an incremental KRAS testing cost of £462, additional drug costs of £3357 and additional administration costs of £1589*'

Are the provisional recommendations a sound and suitable basis for guidance to the NHS?

We have no issues to raise under this heading.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

We are not aware of any such issues.