Introduction

The quality of evidence used by manufacturers in submissions to HTA agencies is an important determinant of a positive appraisal. Head-to-head RCT data is the accepted gold standard source of evidence. In 2008, NICE revised guidelines and added a new section on indirect synthesis methods, indicating an increased acceptance of this methodology by NICE.

The objective of this review was to investigate the factors that affect the outcome of HTA submissions, with a focus on indirect and mixed treatment comparisons. We evaluate previous trends and understand past and evolving influences of methodological factors on submission outcomes. In order to do this, all NICE submissions from 2003 to August 2008 were investigated for the evidence presented, use of analysis type, statistical methodology, and the appraisal outcome.

This poster outlines the approach used in this review, and the key results obtained from the extracted information. The considerations for future submissions are discussed.

Methods

A landscape review was conducted of NICE submission methodologies and appraisal outcomes, with focus on the use of indirect comparison. Key data were extracted from NICE/Evidence Review Group documents for all NICE appraisals (2003-August 2008), including:

- Therapeutic area
- Clinical comparisons made
- For subject intervention vs. placebo/active treatment vs.
- Use of direct/indirect/mixed treatment comparison
- Suitability/criticism of statistical methodologies employed
- Appraisal outcome (recommended/partially recommended/not recommended)

Figure 1 outlines the definitions used in this review in the identification of direct, indirect, and mixed treatment comparisons. For the purposes of data extraction, indirect comparison or mixed treatment comparison must have explicitly been mentioned in an appraisal for the analysis type to be recorded as having been used.

Fig 1: Definition of comparison types

<table>
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<tr>
<th>Type</th>
<th>Description</th>
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<tr>
<td>a. Direct comparison</td>
<td>Informed only by head-to-head RCTs of treatments</td>
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<tr>
<td>b. Indirect comparison</td>
<td>Informed comparative studies of those technologies against a common comparator*</td>
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<tr>
<td>c. Mixed treatment comparison</td>
<td>Informed by both (i) Evidence from head-to-head trials (ii) Trials against a common comparator*</td>
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*RTCs are the preferred evidence source for comparative studies; observational studies can be included but are not advisable due to the lack of benefit from recombination.

Appraisals were categorised as recommended, partially recommended or rejected as follows:

- Recommended - The recommendation did not come with any restrictions or matched exactly the indication or subgroup proposed in the submission
- Partially recommended - The recommendation specified additional criteria for the use of the drug, e.g. a specific patient subgroup
- Rejected - Did not recommend the treatment

This information was then analysed to determine the level of use of indirect comparison over time and therapeutic area, and the influence of this on appraisal outcomes. In addition, a number of case studies were investigated in detail. Case studies were selected in rheumatoid arthritis, osteoporosis, bone metastases and oncology. Key findings and recommendations for submission preparation, with a focus on indirect comparison use, are presented.

Results

Figure 2 illustrates the number of direct and indirect comparisons used in NICE appraisals from 2005 to 2008. Submission for 2008 were considered up to August only, as estimates for the whole of 2008 are not available.

The number of appraisals using indirect comparisons has increased from 2 to 8 between 2005 and August 2008. The proportions of published NICE appraisals mentioning indirect comparisons to total appraisals were 2/7 (2005), 2/18 (2006), 7/21 (2007) and 8/26 to August 2008. There was a relatively large increase between 2005 - 2007 in the number of appraisals that contain indirect comparison (11% to 33%), possibly indicating increased acceptability of this methodology.

Conclusion

NICE has and is likely highly to continue to show a preference for head-to-head trials. However, data from this review supports an increased use of indirect comparison as a source of evidence. The 2008 update to the NICE guidelines reflect this increased acceptability of these methodologies. We can conclude that indirect analysis should be considered where head-to-head data are unavailable or insufficient and as a source of supporting evidence.

It is important that previous criteria of indirect comparison are considered. Rationales for the use of indirect comparisons must be clear. Additionally, to maximise the quality of submissions, analyses must use validated methodologies, manage heterogeneity appropriately and clearly justify decisions and usage of methods and comparisons.

References

2. Details of NICE appraisals published from 2003-2008: http://www.nice.org.uk/Guidance/TA/Published
4. Erbitux for mCRC technology appraisal: http://www.nice.org.uk/Guidance/TA1196

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