Indirect Treatment Comparisons and Network Meta-Analysis: A Review of Manufacturers' Submissions to the NICE Single Technology Appraisal Process (STA)

Matthew Bending, YHEC

John Hutton, YHEC

Clare McGrath, Pfizer Inc.

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Objectives

The objective of this study is to investigate the reporting, characteristics and validity of indirect comparisons (ITC) and network meta-analysis (NM) submitted by manufacturers to the NICE Single Technology Appraisal (STA) process for pharmaceuticals.

Definitions

This study uses the definitions provided in the ISPOR Taskforce working paper for ITC and network meta-analysis (Jansen *et al.* 2011).

- **Network meta-analysis (NM):**

  Evidence consists of *more than* two RCTs connecting *more than* two interventions.

- **Anchored Indirect Treatment Comparison (ITC):**

  The synthesis of data for a medicine that has not been compared in head to head trials but uses data from multiple trials indirectly.

- **Mixed Treatment Comparison (MTC):**

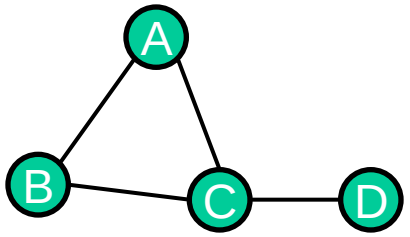
  A synthesis of data that includes RCTs that compare the medicines of interest combining head to head trials and indirect evidence.

NICE Guide Section 5.3.13

NICE provides guidance for use of these types of analysis in manufacturers submission, (NICE, 2008):

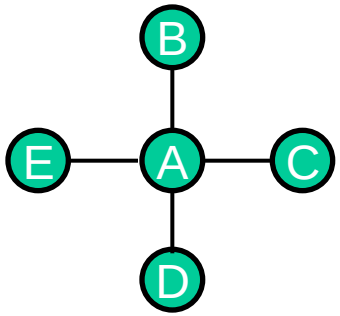
MTC:

Head to head used when available but MTCs can be presented when adding additional information to the base case.



ITC:

If head to head data is unavailable then ITCs can be used to inform the effectiveness for the base case.



Methods

- Search of NICE website for Manufacturer Submission (MS), Evidence Review Group's (ERG) report and guidance for between August 2006 and April 2011 (updated sample).

- A literature review informed the production of a data extraction sheet for the reporting and description of characteristics of ITC/NM submitted to NICE*:

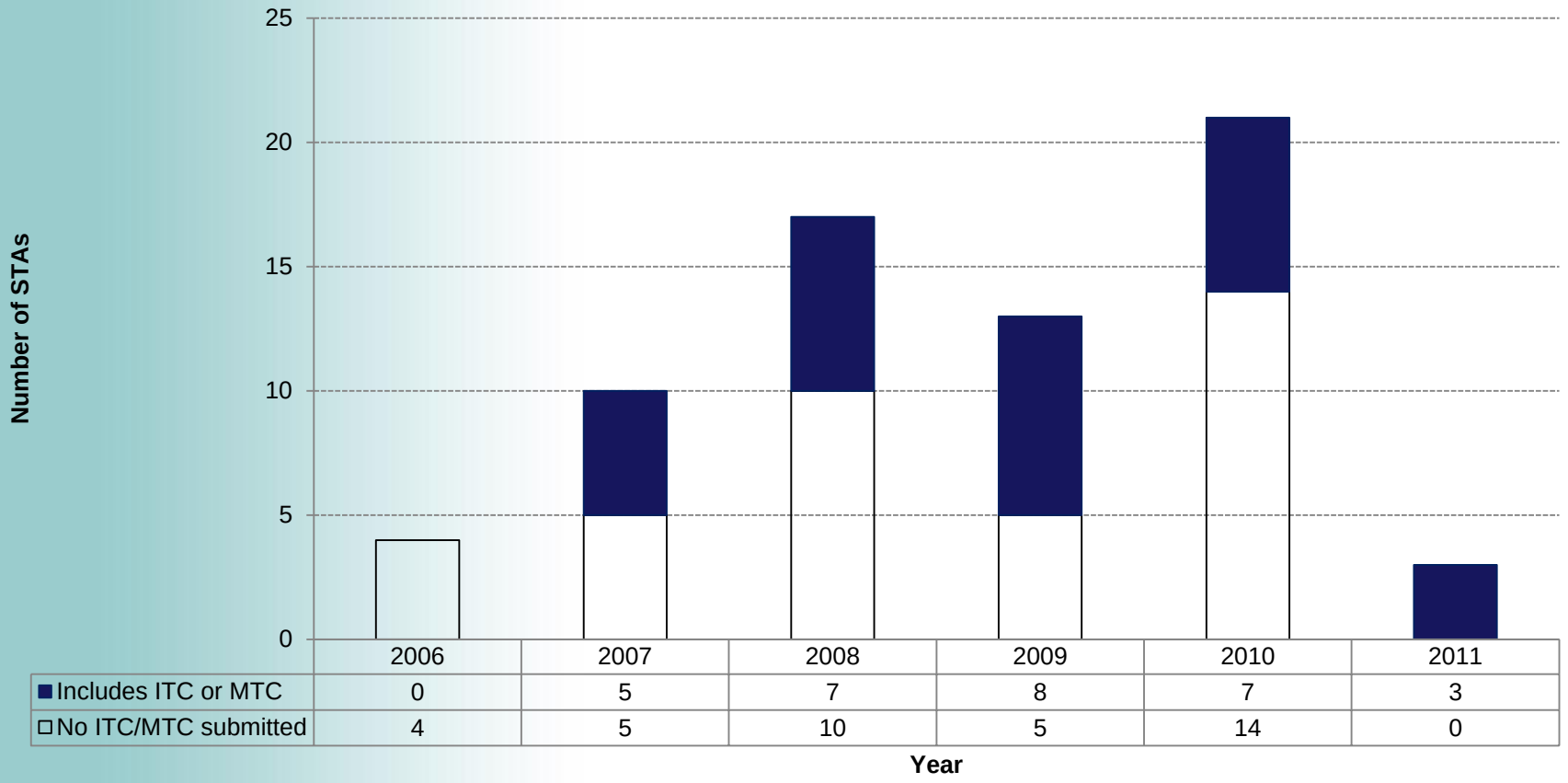
    1. Objective of analysis
    2. Methods of analysis reporting and characteristics
    3. Results of analysis of evidence synthesis
    4. Model diagnostic assessment
    5. External validity of results

- Qualitative documentary analysis of the ERG critiques of the submitted ITC/NM using Atlas.ti 6.2 software.

* Lumley 2002, Song et al. 2003, Sutton et al. 2008, NICE, 2008, Hawkins et al. 2009, Song et al. 2009, Donegan et al. 2010, Dias et al. 2010 and Jansen et al., 2011.

Indirect Comparisons and Network Meta-analysis submitted by Manufacturers to the NICE STA Process

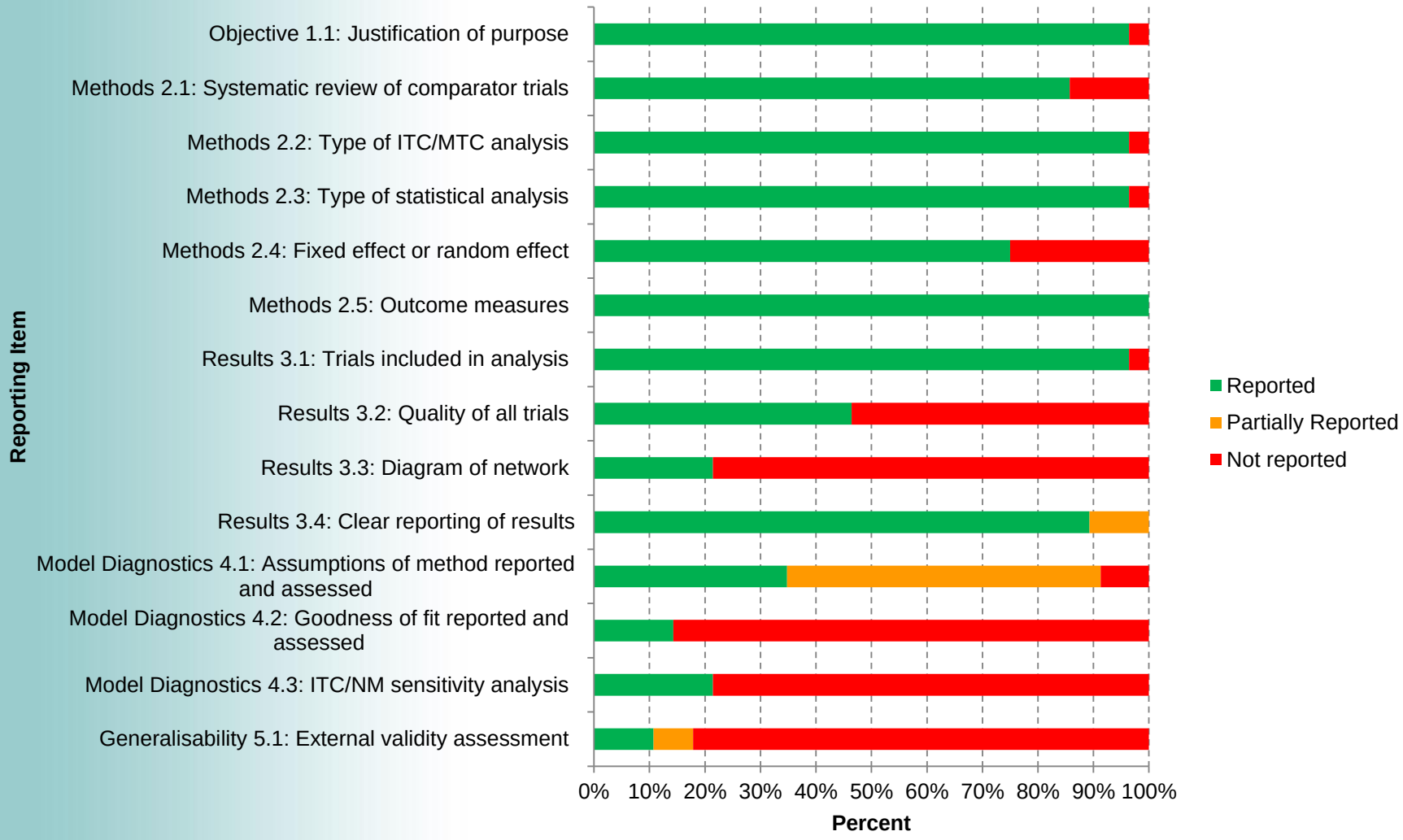
- 44% (30 out of 68) of MS included an ITC or NM.



	2006	2007	2008	2009	2010	2011
Includes ITC or MTC	0	5	7	8	7	3
No ITC/MTC submitted	4	5	10	5	14	0

Results 1:
Reporting of Indirect Treatment Comparison/Network Meta-Analysis in Manufacturer Submission

Reporting in Manufacturers submissions for ITC and NM



Reporting of Underlying Assumptions

	Reporting of Assumptions* §		
	Homogeneity	Similarity	Consistency
Anchored indirect comparison (single trials)	0% (0/2)	100% (2/2)	
Network meta-analysis: Anchored indirect comparison	79% (11/14)	79% (11/14)	
Network meta-analysis: Mixed Treatment Comparison	57% (4/7)	71% (5/7)	14% (1/7)

*Excludes reporting in four naïve indirect comparisons, one unclear comparison and two analyses reported from other publications.
±Assumptions as defined by Song *et al.* (2009).

Results 2:
Description of characteristics of Indirect Treatment Comparisons / Network Meta-Analysis in Manufacturer Submission

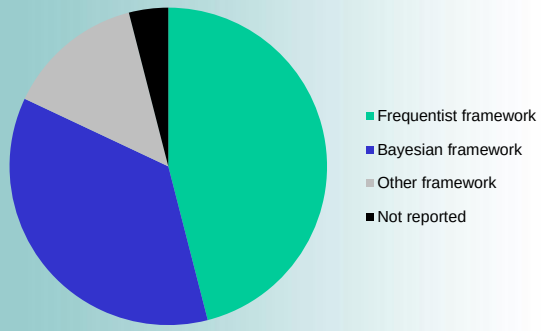
Types of ITC / NM Submitted to NICE in MS

- Manufacturer submission date (Guidance date TA123 –TA215):
  - May 2006 (Jul 2007) – Apr 2010 (Feb 2011)

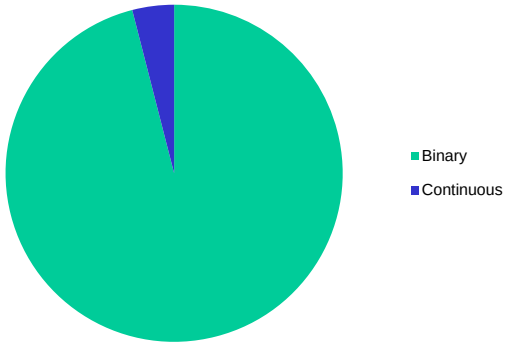
Type	Number (percent)	Direct comparison available	Meta-regression including covariates	Mean number of trials included
Unclear	1 (4%)	0	0	-
Naïve indirect comparison	4 (14%)	1	0	-
Anchored indirect comparison	2 (7%)	0	0	2
Network meta-analysis: Anchored indirect comparison	14 (50%)	2	1	11
Network meta-analysis: Mixed Treatment Comparison	7 (25%)	7	1	17
Total	**28**	**10**	**2**	**13**

Characteristics of ITC / NM Submitted to NICE

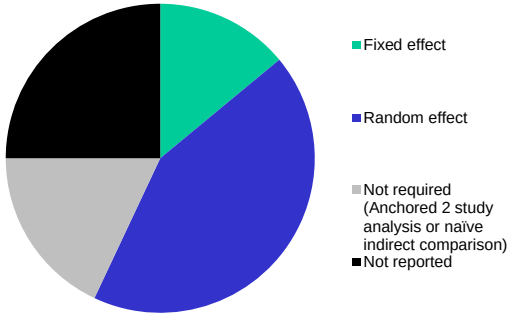
Type of statistical framework



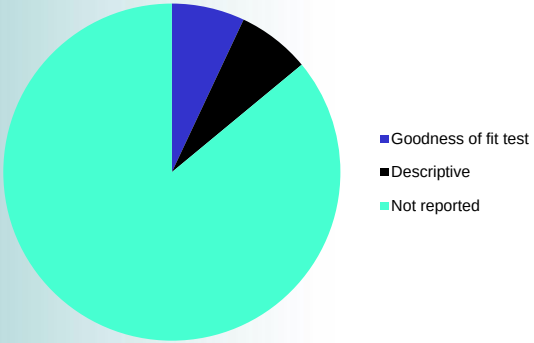
Type of outcome



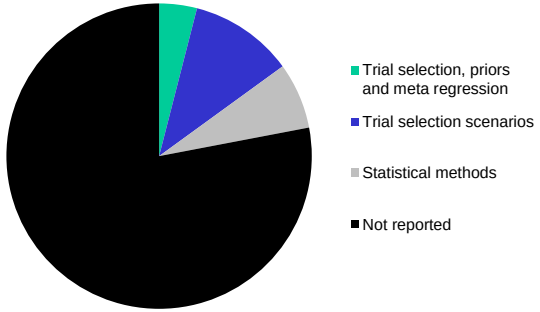
Type of statistical analysis



Model goodness of fit



Model sensitivity analysis



Results 3:
Thematic Analysis of ERG Critiques

Documentary Analysis: Validity of ITC / NM Analysis

- 30 ERG reports included in Atlas.ti software
- Description of characteristics of ERG approach
- ERG reports specific sections critiques of the ITC/NM were analysed:
  - 53 codes for 160 quotations were generated
  - Themes and sub-themes were generated and categorised by strengths and weaknesses

ERG Reports Critique of Manufacturers Submissions

Description	Percent (Number)
ERG states undertaking additional analysis	26% (8/30)
- Reproduced analysis	3
- Alternative trial selection	2
- Alternative search	1
- Using different assumptions	2
ERG uses a checklist designed to assess the conduct of the ITC or NM	7% (2/30)
ERG uses a definition for MTC inconsistent with NICE	13% (4/30)

Summary of Themes from 30 ERG Critiques

Theme	Description	Sub-Themes	
		Strengths of MS	Weaknesses of MS
Reporting	The manufacturers reporting of aspects of the analysis including objective, systematic review, methods, ITC/NM assumptions, model diagnostics and external validity.	Detailed description of systematic review 4 Methods generally well reported 2 Discussion of similarity assumption 1	**Lack of quality assessment of studies 14** **Lack of discussion of assumptions 10** Lack of transparency of methodology 9 Lack of Inclusion/exclusion criteria 7 Search strategy not reported 2
Objective	The justification of the use of ITC or NM in terms of the evidence available and the decision problem. Reference to NICEs guide section 5.13.	Suitable justification of purpose 5	Other organisations published analysis used 2 Purpose not justified 2 Analysis goes beyond scope 1
Appropriateness of Methodology	Justification of the methodology used given the available data.		**Inappropriate application of methodology 7** Rationale for lack of meta-analysis not valid 3 Meta-regression would have been appropriate 1
Internal Validity	The degree of certainty by which the effect observed in the ITC or NM analysis is the result of the intervention (risk of bias). ERG critique of assumptions and data.	Thorough analysis of heterogeneity 1 Useful goodness of fit test performed 1 Useful sensitivity analysis for trial selection 1	**Inappropriate study selection 13** **Concerns relating to similarity assumption 9** Concerns relating to heterogeneity 6 Sparsity of studies included 5 Errors in use of trial data 3 Concerns relating to consistency assumption 1
External Validity	ERGs critique of the generalisability of the analysis to real world patients in England and Wales.		Generalisability of analysis findings 6
Overall Fitness for Purpose	ERG comments on fitness for purpose of the ITC or NM when considering all aspects of validity was specifically referred to.	Reasonable/robust analysis presented 5	Results should be treated with caution 8

Discussion

- ITC/NM submitted by manufacturers have been useful to understand the fitness for purpose of the clinical evidence for NICE decision-making
- Assumptions, model diagnostics and generalisability of ITC/NM were frequently not reported in manufacturer submission
- ERG approaches to critical appraisal of ITC/NM vary across submissions but identify many issues with respect to conduct, especially lack of reporting
- Large variation across submissions in the quality and validity of ITC/NM
- Limitations: Manufacturer submissions lag (2006-2009), reporting, appendices and subjectivity in classification of themes

Conclusion

- ITC and NM analysis has provided additional useful information for NICE appraisals but there has been wide variation in the reporting and validity of analysis performed

- Reimbursement agencies should establish guidelines for the conduct of ITC and MTC to improve quality and reduce variation

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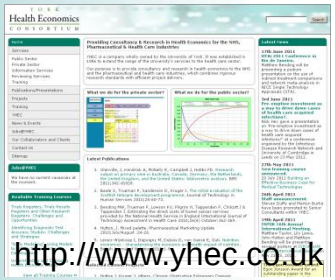
Questions?



http://www.yhec.co.uk

Matthew Bending

matthew.bending@york.ac.uk

University of York, Market Square, Vanbrugh Way, Heslington, York YO10 5NH
Tel: +44 (0)1904 433620
Fax: +44(0)1904 433628

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