Supplementary Data 1: Review Protocol

Field (based on PRISMA-P)	Content
Review question	What is the clinical and cost effectiveness of chemoradiotherapy or surgery with adjuvant treatment for the treatment for N2 stage NSCLC?
Type of review question	Intervention
Objective of the review	To provide clearer guidance regarding the treatment of N2 stage NSCLC. This question was identified during scoping meeting 2. Variation in practice has also been identified.
Eligibility criteria – population/ disease/ condition/ issue/ domain	People with stage N2 M0 NSCLC.
Eligibility criteria – intervention(s)/exposure(s)/ prognostic factor(s)	Surgery with/ without chemotherapy
Eligibility criteria – comparator(s)/control or reference (gold) standard	1. Chemoradiotherapy (radiotherapy and chemotherapy) versus 2. Tri-modality treatment

Outcomes and prioritisation	• Mortality
	  ○ Cancer-related
	  ○ Treatment-related
	  ○ All-cause
	• Quality of life (as measured by QoL instrument, for example)
	  ○ ECOG score
	  ○ EORTC score
	  ○ EQ-5D
	• Length of stay
	  ○ hospital
	  ○ ICU
	• Exercise tolerance
	• Adverse events
	  ○ Oesophagitis, pneumonitis, sepsis (grading)
	  ○ Dyspnoea
	  ○ Hypoxia and need for home oxygen
	  ○ Stroke
	  ○ Cardiovascular disease
	• Treatment-related dropout rates
	• Pain (continuous pain scales and/ or proportions of people in pain)

Eligibility criteria – study design	• RCT data. • Systematic reviews of RCTs
Other inclusion exclusion criteria	• Non English-language papers • Unpublished evidence/ conference proceedings
Proposed sensitivity/sub-group analysis, or meta-regression	No subgroup analysis identified

Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See appendix B.
Information sources – databases and dates	No date limit. See appendix C. Main Searches: • Cochrane Database of Systematic Reviews – CDSR • Cochrane Central Register of Controlled Trials – CENTRAL • Database of Abstracts of Reviews of Effects – DARE • Health Technology Assessment Database – HTA • EMBASE (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) Citation searching will be carried out in addition on analyst/committee selected papers. The search will not be date limited because this is a new review question.
Identify if an update	Update. Original Question (linked): What is the most effective treatment for patients with resectable non-small cell lung cancer? **Recommendations that may be affected:** 1.4.27 Patients with stage I or II NSCLC who are medically inoperable but suitable for radical radiotherapy should be offered the CHART regimen. **[2005]**
Author contacts	Guideline update
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C
Data collection process – forms/ duplicate	A standardised evidence table format will be used, and published as appendix G (clinical evidence tables) or H (economic evidence tables) of the full guideline.
Data items – define all variables to be collected	For details please see evidence tables in appendix G (clinical evidence tables) or H (economic evidence tables) of the full guideline.

Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ For further detail see Appendix B.
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	For details please see the methods chapter of the full guideline. See appendix B.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. See appendix B.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual See appendix B.
Rationale/ context – Current management	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by NICE Guideline Updates Team and chaired by Gary McVeigh in line with section 3 of Developing NICE guidelines: the manual. Staff from NICE Guideline Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
PROSPERO registration number	N/A

Supplementary Data 2: Economic model and scenario analyses results (ICERs) exploring plausible variations in the model's input parameters

Scenario	CRS vs CR	CS vs CR	CRS vs CS	Notes
Base Case (5y, FE, disc)	£19,829	£74,925	£4,151	
Base Case PSA	£19,017	£77,698	£3,973	Based on the mean of 5,000 iterations
5Y Random Effects	£20,082	£158,757	£4,064	Random rather than fixed effects NMAs used for first 5 years
No adverse events	£21,268	£68,004	£7,968	Adverse events = 0 for all treatments
Adverse events from NMA	£19,009	£72,704	£3,729	Based on NMA (see appendix J) rather than pairwise data
No treatment disutility	£18,877	£60,509	£4,163	Surgical patients suffer no post-surgery utility decrement
No long term utility decrement	£19,689	£72,305	£4,156	Standard age related utility decrements not applied
Exponential survival curve	£20,129	£81,291	£4,142	Survival in patients alive at 5 years modelled using an Exponential curve
Long term PFS costs = 100%	£21,787	£84,893	£3,829	Costs for patients surviving 5 years progression free = those within the first 5 years
Long term PFS costs = 50%	£20,563	£78,663	£4,030	Costs for patients surviving 5 years progression free half those within the first 5 years
% undergoing surgery MA = all trials	£22,148	£80,950	£5,521	% patients dropping out of surgery after chemotherapy derived from all trials in NMA
% undergoing surgery = 100%	£26,417	£100,174	£6,088	% patients dropping out of surgery after chemotherapy = 0%
Discount rate = 0%	£16,093	£33,397	£4,250	No economic discounting
4y Fixed Effects NMA	£20,205	£128,347	£6,185	NMAs are from 4 year outcomes rather than 5 year. Survival continues from 4 years
Progs that are deaths set equal	£21,178	£78,732	£4,800	% of progressions that are in fact deaths set equal among treatments
PFS Utility = 0.72	£21,214	£80,927	£4,429	Progression free utility set to lowest value from literature review
PFS Utility = 0.83	£18,770	£70,411	£3,937	Progression free utility set to highest value from literature review
Max util, Max decr between PFS and PPS	£19,595	£74,711	£4,091	PFS utility and utility decrement from progression set to highest available values
Min util, Min decr between PFS and PPS	£20,250	£75,906	£4,248	PFS utility and utility decrement from progression set to lowest available values
OR of survival set equal	£41,105	dominated	£3,805	OR of survival = 1 for CS and CRS vs CR

Cost of Surgery = CC 6+	£30,062	£123,274	£3,537	Assume cost of surgery = to most complex in class
Cost of Surgery = CC 0-2	£15,433	£54,155	£4,414	Assume cost of surgery = to least complex in class
Cost of Progressed State Halved	£27,201	£85,067	£10,734	Monthly cost of the post progression state halved
Eberhardt baseline for NMAs	£12,281	dominated	£716	Baseline population CR data from Eberhardt 2015

Supplementary Figure: diagram of economic model