HTA NO 16/58/01: EVALUATION OF THE CLINICAL AND COST-EFFECTIVENESS OF EVEROLIMUS, NIVOLUMAB, AXITINIB, SORAFENIB AND SUNITINIB IN RENAL CELL CARCINOMA

FINAL PROTOCOL

Date: 24/05/2016

1 TITLE OF THE PROJECT

Evaluation of the clinical and cost-effectiveness of everolimus, nivolumab, axitinib, sorafenib and sunitinib in previously treated renal cell carcinoma

2 TAR TEAM AND PROJECT 'LEAD'

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3 PLAIN ENGLISH SUMMARY

In 2012 kidney cancer was the eighth most common cancer in the UK, accounting for 3% of all new cases.[(1)] Around 75% of people diagnosed with kidney cancer are over 60 years old, while this condition is rare in people under 50.[(2)] Renal cell carcinoma (RCC) is the most common type of kidney cancer, with over 80% of kidney cancer cases diagnosed as RCC in the UK.[(3)] Around 40% of people diagnosed with RCC are stage 1. This means that the tumour is contained entirely within the kidney and the prognosis is generally good with 80% of stage 1 RCC patients surviving for 5 years or more after diagnosis.[(1)] Most patients have

more advanced RCC at diagnosis, with 25% of patients being diagnosed stage 3 and 20% of patients having stage 4 disease.[1] In stage 3 and stage 4 of RCC the cancer cells have spread to a lymph node (advanced disease) or to the tissues around the kidney and may have spread to other organs in the body (metastatic disease).[1] If the cancer has spread out of the kidney a complete cure may not be possible, and the goal of treatment regimens is to slow the cancer's progression and treat symptoms.[4] Approximately 60% of patients with stage 3 RCC will survive for 5 years or more after diagnosis, while only around 5% of patients with stage 4 disease will survive for 5 years or more after diagnosis.[1]

The main treatments for RCC include nephrectomy, embolisation, radiotherapy, targeted therapies and (less frequently) immunotherapy. Immunotherapy treatments are now rarely used to treat advanced kidney cancer because targeted therapies tend to be more effective in controlling the condition, and immunotherapy can sometimes cause serious side effects. Targeted therapies are designed to target and interrupt the functions needed by cancer to grow and spread. At present, targeted therapies recommended by the National Institute for Health and Care Excellence (NICE) for people with advanced or metastatic RCC are sunitinib[5] and pazopanib[6] for first line treatment and axitinib[7] for second-line treatment. They're available on the NHS for people who are still relatively healthy and have advanced kidney cancer, or kidney cancer that's spread to other parts of their body.

The aim of this project is to review the clinical and cost-effectiveness of axitinib, everolimus, nivolumab, sorafenib and sunitinib for treated advanced or metastatic RCC. The medical benefit and risks associated with these treatments will be assessed and compared across the treatments and against best supportive care for advanced or metastatic RCC. This project will also include an assessment of whether these drugs are likely to be considered good value for money for the National Health Service (NHS).

4 DECISION PROBLEM

4.*1 Purpose*

The purpose of this technology assessment will be to appraise the clinical and cost-effectiveness of axitinib, everolimus, nivolumab, sorafenib and sunitinib for treated advanced or metastatic RCC in line with their respective or for nivolumab, the anticipated marketing authorisations.

4.2 Interventions

Axitinib (Inlyta®, Pfizer) is an inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases. It has a marketing authorisation in the UK for the treatment of adults with advanced RCC after failure of previous treatment with sunitinib or a cytokine.

Everolimus (Afinitor®, Novartis) is an inhibitor of mammalian target of rapamycin (mTOR). It has a marketing authorisation in the UK for the treatment of people with advanced RCC, whose disease has progressed on or after treatment with VEGF-targeted therapy.

Nivolumab (Opdivo®, Bristol-Myers Squibb) is a human immunoglobulin G4 monoclonal antibody that binds to the cell surface receptor programmed death-1(PD-1; a negative immuno-regulatory protein), thereby activating an immune response to tumour cells. Nivolumab does not currently have a marketing authorisation in the UK for treating renal cell carcinoma. It has been studied in clinical trials, compared with everolimus, in adults with advanced or metastatic clear-cell RCC who have received previous anti-angiogenic therapies. On the 25h February 2016, the committee for Medical Products for Human Use (CHMP) gave a positive opinion on nivolumab recommending extending the use of nivolumab to include the treatment of adult patients with advanced RCC who have received prior therapy. In addition, in November 2015 nivolumab received marketing authorisation in the US for treatment of advanced RCC in patients who have received prior anti-angiogenic therapy.

Sorafenib (Nexavar®, Bayer/Onyx) is a multikinase inhibitor. It has a marketing authorisation in the UK for the treatment of people with advanced RCC whose disease has failed previous interferon-alpha or interleukin-2 based (cytokine agents) therapy, or who are considered unsuitable for such therapy.

Sunitinib (Sutent®, Pfizer) is an inhibitor of several receptor tyrosine kinases. It has a marketing authorisation in the UK for the treatment of advanced/metastatic RCC in adults.

All the technologies apart from Nivolumab are given orally. Nivolumab is given intravenously.

4.3 Place of the interventions in the treatment pathway

Currently only axitinib is recommended for second-line treatment of advanced or metastatic RCC in patients who have received previous cytokine or VEGF-targeted therapy. Sorafenib and sunitinib both have a market authorisation for second-line treatment of advanced of metastatic RCC, however, neither drug are currently recommended by NICE for this indication. Nivolumab is also anticipated to receive an extension to its current UK marketing

authorisation to enable it to be used in the treatment of adult patients with advanced RCC who have received prior therapy, and it is currently undergoing appraisal by NICE for use in this indication.

Everolimus is also not recommended by NICE but was available in England through the Cancer Drugs Fund (CDF), however the drug was removed from the CDF on 4th November 2015, with the exception of patients contraindicated to second-line axitinib or patients with excessive toxicity to axitinib necessitating discontinuation of axitinib within 3 months of starting therapy if there is no evidence of disease progression by then).

This systematic review will consider the clinical and cost-effectiveness evidence for axitinib, sorafenib and sunitinib for advanced or metastatic RCC patients who have received previous cytokine therapy (aldesleukin or interferon alfa) and also the evidence available for axitinib, nivolumab, sunitinib and everolimus for advanced or metastatic RCC patients who have received previous VEGF-targeted therapy (which may include pazopanib, bevacizumab, sorafenib, sunitinib or axitinib).

4.4 Relevant comparators

For patients who have received previous cytokine therapy (aldesleukin or interferon alfa) the relevant comparators are:

- Axitinib;
- Sorafenib;
- Sunitinib;
- Best supportive care.

For patients who have received previous VEGF-targeted therapy the relevant comparators are:

- Axitinib;
- Everolimus;
- Nivolumab;
- Sunitinib;
- Best supportive care.

To note is that any cost-effectiveness analysis undertaken will only consider interventions and comparators within their marketing authorisation, and for nivolumab the anticipated marketing authorisation will be used.

4.5 Population and relevant subgroups

The population of interest to the current appraisal is people with previously treated, advanced or metastatic RCC. If the evidence allows the following subgroups will be considered:

- Previous treatment;
- Patients' prognostic scores (for example ECOG or Motzer).

4.6 Outcomes to be addressed

If data allow, outcome measures will include:

- Overall survival;
- Progression-free survival;
- Response rates (objective response rate, complete response rate, partial response rate);
- Adverse effects of treatment (Common Terminology Criteria for Adverse Events v3.0 (CTCAE) (2006)[8] grade 3 or higher);
- Health-related quality of life (HRQoL)
- Cost-effectiveness.

5 REPORT METHODS FOR SYNTHESIS OF EVIDENCE OF CLINICAL EFFECTIVENESS

This systematic review will include a review of axitinib, sorafenib, and sunitinib for people who have received previous cytokine therapy (aldesleukin or interferon alfa), and axitinib, nivolumab, everolimus and sunitinib for people who have received previous vascular endothelial growth (VEGF)-targeted therapy for the treatment of advanced and/or metastatic RCC. The systematic review will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination.[9]

5.1 Search strategy

This systematic review will include a review of axitinib, sorafenib and sunitinib for patients who have received previous cytokine therapy (e.g. aldesleukin or interferon alfa), and axitinib, everolimus, nivolumab and sunitinib for people who have received vascular endothelial growth factor-targeted (VEGF) therapy.

Should the randomised evidence base be insufficient to inform the decision problem that is the focus of this report, a search for comparative non-randomised trials will be conducted. Any non-RCT evidence identified will be considered for suitability and recommended methods used to minimise the introduction of bias.[10]

To identify relevant RCTs, a comprehensive search strategy will be designed and used to search multiple electronic databases including MEDLINE, EMBASE, Cochrane Library (CENTRAL), and DARE. Bibliographies of retrieved studies (RCTs and systematic reviews) identified as relevant will be manually reviewed for potentially eligible studies. On-going clinical trials will be identified by searching clinical trial registries, including ClinicalTrials.gov and the EU Clinical Trials Register. The Index to Scientific and Technical Proceedings will be searched to identify relevant conference proceedings. Appropriate organisational websites, databases, and registers will also be searched. In addition, experts in the field will be contacted with a request for details of published and unpublished studies of which they may have knowledge.

The search strategy will combine terms for the interventions or comparators of interest with terms for the target condition (RCC). Additional search terms of interventions outside the scope of this report that may be relevant for creating a connective network diagram will be used. However, trials of interventions not listed in the scope will only be included if they are needed to create a network linking the interventions and comparators listed in the scope.

No date or language restrictions will be applied to the search strategy. Full details of the terms used in the scoping search are presented in Appendix 9.1.

5.2 Study selection criteria and procedures

Two reviewers will independently screen all titles and abstracts according to the inclusion criteria (see Table 1). Full paper manuscripts of any titles/abstracts that may be relevant will be obtained where possible and the relevance of each study assessed. Discrepancies will be resolved by consensus, with involvement of a third reviewer when necessary.

Table 1. Inclusion criteria

Inclusion criteria	
Study design	RCTs (comparative non-RCTs will be considered when RCT evidence is insufficient to inform decision problem)
Population	Patients with previously treated, advanced or metastatic RCC
Interventions	For people who have received previous cytokine therapy (aldesleukin or interferon alfa): • Axitinib • Sorafenib • Sunitinib For people who have received previous VEGF-targeted therapy: • Axitinib • Everolimus • Nivolumab • Sunitinib
Comparators	• The interventions listed above compared with each other • Best supportive care
Outcome	• Overall survival • Progression free survival • Response rates • Adverse effects of treatment • HRQoL
Abbreviations used in table: HRQoL, health-related quality of life; RCC, renal cell carcinoma; RCT, randomised controlled trial; VEGF, vascular endothelial growth factor	

Preclinical studies and those conducted in animals, and narrative reviews, editorials, opinions and case reports will be excluded from the review.

5.3 Subgroups

If the evidence allows, data will be analysed according to the following subgroups:

- Previous treatment;
- Patients' prognostic scores (for example ECOG or Motzer).

5.4 Outcomes

Data on the following outcome measures will be assessed:

- Overall survival;
- Progression-free survival;
- Response rates;
- Adverse effects of treatment;

- HRQoL.

5.5 Data extraction strategy

Full paper manuscripts of any included reference will be obtained where possible. Data will be extracted independently by two reviewers using a standardised data extraction form (see Appendix 9.2). Information extracted will include details of the study's design and methodology, baseline characteristics of participants and results including any adverse events reported. Where there is incomplete information the study authors will be contacted to gain further details, allowing about two weeks' timeframe. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

5.6 Quality assessment strategy

The quality of the clinical effectiveness studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted. The study quality will be assessed according to recommendations by the NHS Centre for Reviews and Dissemination[9] and *Cochrane Handbook for Systematic Reviews of Interventions*.[11] This will include assessing the following factors:

- Random sequence generation;
- Allocation concealment;
- Blinding of participants, personnel and outcome assessment;
- Incomplete outcome data;
- Selective outcome reporting;
- Other bias.

5.7 Methods of analysis/synthesis

Extracted data and quality assessment for each study of clinical effectiveness will be presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed. Should sufficient comparable data be identified, standard pair-wise comparisons and/or mixed-treatment comparisons (MTC) will be performed to evaluate the clinical effectiveness.

Treatment effects will be presented as odds ratios for dichotomous data, (weighted) mean differences for continuous data or as hazard ratios where appropriate. Mixed-treatment comparisons will be performed using a Bayesian (Markov Chain Monte Carlo (MCMC) simulation.[12] Pair-wise meta-analysis will be carried out using Comprehensive Meta Analysis software, with the use of fixed- and/or random-effects model appropriate to the assembled datasets. Clinical and methodological heterogeneity of potentially included studies will be assessed prior to data analysis. Statistical heterogeneity will be investigated to identify plausible potential causes based on the studies analysed.

6 REPORT METHODS FOR SYNTHESISING EVIDENCE OF COST-EFFECTIVENESS

The purpose of this report will be to assess the cost-effectiveness of axitinib, everolimus, nivolumab, sorafenib and sunitinib within their marketing authorisations (anticipated marketing authorisation for nivolumab) for the treatment of advanced or metastatic RCC in the UK. These interventions will be compared with each other and with best supportive care used in the NHS. This overarching objective will be met through identification and appraisal of:

- Published economic evaluations from the literature;
- HRQoL studies of advanced or metastatic RCC including safety data;
- UK specific resource use data. Non-UK sources will be considered if there is insufficient UK specific information.

Should the published or submitted economic evaluations prove insufficient to answer the review question; an independent *de novo* economic model will be developed.

6.1 Search strategy

The cost-effectiveness search will aim to identify full economic evaluations, costing studies and HRQoL studies. The following electronic databases will be searched in order to identify economic evaluations and quality of life studies for the interventions considered:

- MEDLINE (Ovid);
- EMBASE (Ovid);
- Database of Reviews of Effects (DARE);
- NHS Economic Evaluations Database (NHS EED).

Databases will be searched from inception for evidence on all the relevant interventions.

As an example, the details of the MEDLINE search strategy are presented in full in Appendix 9.1. The search strategy will combine terms capturing the interventions or comparators of interest and the target condition (RCC). Health economic and quality of life search terms will be applied to capture the study designs of interest (cost-effectiveness, cost and quality of life, health state utility values [HSUVs]). No language (to assess volume of foreign language studies available), setting or country restrictions will be applied to the search strategy. In addition, experts in the field will be contacted with a request for details of published and unpublished studies of which they may have knowledge. Furthermore, identified systematic reviews and companies' submissions will be searched for additional references.

6.2 Inclusion and exclusion criteria

The titles and abstracts of papers identified through the searches outlined above will be independently assessed for inclusion by two reviewers using the following criteria:

Inclusion criteria:

- All economic evaluations (cost-effectiveness, cost-utility, cost-benefit, cost-consequence or cost-minimisation);
- Any setting (to be as inclusive as possible);
- Intervention or comparators:
    - Axitinib
    - Everolimus
    - Nivolumab
    - Sorafenib
    - Sunitinib
- Study outcomes reported in terms of life-years gained (LYG) or quality adjusted life years (QALYs);
- Full publications in English (numbers of relevant non-English studies will be reported);
- Quality of life studies in RCC;
- Costing/resource use studies in RCC (for resource use review).

Exclusion criteria:

- Abstracts with insufficient methodological details;

- Systematic reviews;
- Studies not available in English language.

Sources of evidence reporting data for additional interventions considered relevant in advanced and metastatic RCC treatment will be identified in the systematic search. These sources however will not be data-extracted and included in the literature review unless:

- They report data of special interest or relevance, or;
- The evidence already collected is not considered sufficient.

The additional interventions considered are: bevacizumab, interferon-α, pazopanib, temsirolimus and tivozanib.

6.3 Data extraction strategy

Data will be extracted by one reviewer using a standardised data extraction table and checked by a second reviewer for accuracy. Disagreement will be resolved by discussion, however, if no consensus is reached, a third reviewer will be consulted. In cases where there are missing data or unclear reporting in the published or submitted economic evidence or quality of life studies, attempts will be made to contact authors. Studies published in the UK will be reported in greater detail than non-UK studies as they are more likely to be relevant to the NHS. Tables 2 and 3 exemplify the health economic evaluation and quality of life data that will be sought from each study. In addition, the reason for exclusion of each excluded study will be documented (Table 4).Table 2. Health economic evaluation data extraction table

Author, year, country	**Perspective, discounting & cost year**	**Model type**	**Patient population**	**Intervention/ comparator**	**Outcomes**	**Results ICER (per QALY gained) incl. uncertainty**
Reviewer's comments:						
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year						

Table 3. Quality of life data extraction table

Author, year, Country	**Sample size**	**Patient population**	**Instrument (Valuation)**	**Utility results**
Reviewer's comments:				

Table 4. Data exclusion table

Bibliographic reference	Reasons for exclusion
Reviewer's comments:	

6.4 Quality assessment strategy

All published economic evaluations identified within the review will be subject to critical appraisal. The methodological quality of each economic evaluation will be assessed against the NICE reference checklist for economic evaluations[10] together with the Philips checklist[13] on mathematical models used in technology assessments (see Appendix 9.3). Each economic evaluation will be assessed by one health economist and the details of the assessment checked by a second health economist.

6.5 Methods of analysis

Published and submitted economic evaluations

A narrative summary and accompanying data extraction table will be presented to summarise evidence from published or submitted economic evaluations.

Economic modelling

Should the economic evidence identified prove insufficient to answer the research question; a *de novo* economic model will be developed in Microsoft Excel®. The structure of the *de novo* model will be informed by economic evaluations identified in the published literature and clinical expert opinion.[14, 15] All structural assumptions will be documented and accompanying rationales provided. It is anticipated that the model used in the 2009 NICE RCC Multiple Technology Appraisal (MTA) will be the most informative in the development of any *de novo* economic evaluation.[16] The clinical effectiveness parameters required for the economic model will be informed by the review of clinical effectiveness discussed in Section 5. Parameters such as estimates of quality of life (utility data) will be informed by the published literature, identified in the review. In cases where parameters required to populate the model are not available from published studies or company submissions, expert clinical opinion will be considered.

The cost-effectiveness of the interventions will be estimated in terms of an incremental cost per additional QALY gained, as well as the incremental cost per LYG. As appropriate, cost data will be obtained from NHS reference costs[17], British National Formulary[18], Unit Costs of Health and Social Care[19] or company submissions. Costs will consist of direct medical

costs (e.g. drug costs and cost of adverse events, monitoring and administering costs) and direct non-medical costs (e.g. costs of healthcare professional). Resource use and costs will be valued from the NHS and Personal Social Services (PSS) perspective. Both costs and outcomes will be discounted at 3.5% per annum after the first year in accordance with NICE methods guidance.[10] The time horizon for the economic analysis will be long enough to reflect any differences in costs or outcomes between the technologies under comparison.

6.6 Methods for estimating quality of life

Ideally, evidence of the impact of axitinib, everolimus, nivolumab, sorafenib and sunitinib on patients' quality of life will be available directly from identified trials. In the absence of such evidence, any *de novo* economic model may use indirect evidence on quality of life from alternative literature sources, such as related technology appraisals or clinical guidelines. In accordance with NICE methods guidance, utility values will be taken from studies that have been based on "public" preferences elicited using a choice-based method.[10]

6.7 Analysis of uncertainty

Extensive sensitivity analysis will be undertaken to explore uncertainty. Probabilistic sensitivity analysis (PSA) will be undertaken, by which all relevant input parameters will be entered as probability distributions and Monte Carlo simulations will be run to reflect uncertainty in the model's results. In addition, uncertainty will also be explored through one-way sensitivity analysis. The outputs of the PSA will be presented in the cost-effectiveness plane and through the use of cost-effectiveness acceptability curves. One way sensitivity analysis outputs will be presented in tables and tornado diagrams. Where possible, uncertainty pertaining to the structural assumptions used will be assessed in scenario analyses using alternative structural assumptions. If data permits, the impact of patient heterogeneity (e.g. previous RCC treatments received) on cost-effectiveness results will be explored in subgroup analyses.

7 EXPERTISE IN THIS TAR TEAM

The BMJ-TAG is one of the Centres of Excellence identified by NIHR to undertake HTA. As a team dedicated to meeting contractual obligations to the NIHR, the BMJ-TAG has a strong record of submission of high-quality reports to tight deadlines. A brief description of the experience of the individual members of the BMJ-TAG who will contribute to this project is provided.

Head of Clinical & Economic Evidence

Dr Steve Edwards DPhil MSc BSc (Hons)

Steve was brought into the BMJ to form the BMJ-TAG. Since April 2011, the group has supported national decision making by completing research projects for NICE and NIHR. Personally, Steve has been involved in conducting systematic reviews and health economic evaluations in a range of therapeutic areas including cardiovascular, CNS, gastroenterology, infection, oncology, and respiratory medicine. His interests are in the use of the best available evidence for decision making with an emphasis on the design and conduct of clinical trials, systematic reviews, meta-analyses, network meta-analyses and their subsequent use in economic evaluations. His postgraduate research in this area at the University of Oxford resulted in him being awarded the first doctorate of evidence based health care. In addition, Steve is an Honorary Senior Lecturer in the Faculty of Public Health and Policy, London School of Hygiene & Tropical Medicine, a standing member of the NICE Diagnostics Advisory Committee, and a member of the Cochrane Statistical Methods Group, and the Campbell & Cochrane Economics Methods Group.

Health Technology Assessment (HTA) Analysts

Dr Charlotta Karner PhD MSc, HTA Analysis Manager

Since 2011 Charlotta has developed, conducted, and published over 9 systematic reviews as a member of the Cochrane Airways Group. She has worked in a variety of conditions but has a special interest in pharmacological interventions for chronic obstructive pulmonary disease and asthma. Charlotta has also conducted primary research to understand the role of Transient Receptor Potential channels in airway smooth muscle cells. Charlotta has an active interest in translating complex research concept into a format suitable for the general public.

Dr Victoria Wakefield MBChB, Senior HTA Analyst

Vicky has a clinical background with relevant experience in the fields of general surgery, general medicine, general practice, paediatrics and orthopaedic surgery. Vicky also has experience in the critical appraisal of clinical studies and over the last year has contributed to the publication of systematic reviews in a variety of clinical areas. She also has experience in the process and use of clinical audit to review current clinical practice within both primary and secondary care settings.

Dr George Osei-Assibey PhD, HTA Analyst

George has conducted over 20 systematic reviews since 2005 as a PhD student, post-doctoral fellow, and as a senior analyst in a healthcare consultancy for the pharmaceutical sector. He has authored 7 publications in systematic reviews of which three are based on meta-analysis. His systematic review experience covers several disease areas including obesity, diabetes, cardiovascular disease, breast cancer, COPD, asthma, chronic myeloid leukaemia, actinic keratosis, venous thromboembolism, malnutrition.

Health Economists

Andrea Berardi MSc BSc, Health Economics Manager

Andrea is a health economist with a background in statistics and biostatistics. Prior to joining the BMJ Technology Assessment Group he has worked as a consultant, developing health economic evaluations for technologies in a wide range disease areas and based in several different countries. His main interests are in health economics modelling and programming, Bayesian methods in health economics and evidence synthesis.

Mariana Bacelar MSc BSc, Senior Health Economist

Mariana has a BSc in Economics and a MSc in Health Economics. Prior to joining the BMJ Technology Assessment Group, Mariana has been involved in conceptualising and developing Public Health economic models for organisations such as NICE and the European Commission; and providing health economics advisory services to various organisations, including not-for-profit companies. Mariana has been involved in Health Technology Assessment since 2013 and her main interests are in heath economics modelling and the implementation of HTA programmes in different countries. Mariana has recently participated in a project in Brazil, helping to develop the country's HTA programme.

Fatima Salih MSc BDS, Health Economist

Fatima is a qualified dentist with a Masters in Public Health/Health Economics and over 5 years' experience in epidemiological and health services research in various organisations, including the NHS. She also has experience in assessing the effectiveness and cost-

effectiveness of public health programmes, in addition to their implementation and evaluation in the field. Fatima has previously contributed to developing evidence-based infection control guidelines for clinical and community settings. She is particularly interested in projects utilising innovative methods to improve population health.

Recent publications from the team members

Edwards SJ, Osei-Assibey G, Berardi A, et al. Nivolumab for previously treated advanced or metastatic renal cell carcinoma. BMJ Technology Assessment Group, 2016.

Edwards SJ, Karner C, Berardi A, et al. Nivolumab in combination with ipilimumab for advanced melanoma. BMJ Technology Assessment Group, 2016.

Edwards SJ, van Velthoven MH, Berardi A, et al. Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma. BMJ Technology Assessment Group, 2016.

Edwards SJ, Mavranezouli I, Osei-Assibey G, et al. VivaScope 1500 and 3000 systems for detecting and monitoring skin lesions: a systematic review and economic evaluation. A Diagnostic Assessment Report. BMJ-TAG, London. 2015.

Edwards SJ, Crawford F, Wakefield V, et al. Edoxaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism: A Single Technology Appraisal. BMJ-TAG, 2015.

Edwards SJ, Wakefield V, Mavranezouli I, et al. Dexamethasone intravitreal implant for diabetic macular oedema: A Single Technology Appraisal. BMJ-TAG, 2014.

Barton S, Karner C, Salih F, Baldwin DS, Edwards SJ. Clinical effectiveness of interventions for treatment-resistant anxiety in older people: a systematic review. Health Technology Assessment 2014; 18: Number 50.

Edwards SJ, Karner C, Trevor N, et al. Dual-chamber pacemakers for treating symptomatic bradycardia due to sick sinus syndrome without atrioventricular block: A Multiple Technology Appraisal. BMJ-TAG, London, 2014.

Thurgar E, Barton S, Karner C, Edwards SJ. Clinical and cost effectiveness of interventions for the treatment of anogenital warts: systematic review and economic evaluation. BMJ-TAG, 2014.

Edwards S, Wakefield V, Thurgar E, et al. Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism: A Single Technology Appraisal. BMJ-TAG, 2014.

External Clinical Expert Advisors

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Consultant Medical Oncologist specialising in ovarian cancer, kidney cancer, melanoma, immunotherapy, targeted therapy and gene therapy.

Relevant publications

Gore ME, Bellmunt J, Eisen T, et al. Assessing the impact of evolving evidence in renal cell carcinoma treatment: an update of the Renal Cell Carcinoma Appropriateness-based Treatment Toolkit (ReCATT) Eur J Cancer. 2014; 50(18):3153-60.

Kovac M, Navas C, Horswell S, et al. Recurrent chromosomal gains and heterogeneous driver mutations characterise papillary renal cancer evolution. Nat Commun. 2015; 6:6336.

Kasenda B, Larkin J, Gore M. Immunotherapies in Early and Advanced Renal Cell Cancer. Prog Tumor Res. 2015; 42:1-10.

Porta C, Gore ME, Rini BI, et al. Long-term Safety of Sunitinib in Metastatic Renal Cell Carcinoma. Eur Urol.2015:S0302-2838.

Gore ME, Szczylik C, Porta C, et al. Final results from the large sunitinib global expanded-access trial in metastatic renal cell carcinoma. Br J Cancer.2015; 113(1):12-9.

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Consultant Medical Oncologist with special interest in urological oncology (renal, prostate, bladder cancers)

Relevant publications

Gerlinger M, Quezada SA, Peggs KS, et al. Ultra-deep T cell receptor sequencing reveals the complexity and intratumour heterogeneity of T cell clones in renal cell carcinomas. J Pathol. 2013 Dec;231(4):424-32.

Khattak MA, Bakr F, Krzystanek M, et al. Prognostic and predictive markers in metastatic renal cell carcinoma. J Clin Oncol. 2013 1;31(7):971.

Khattak MA, Fisher RA, Pickering LM et al. Endobronchial metastases from renal cell carcinoma: a late manifestation of the disease with an increasing incidence. BJU Int. 2012;110(10):1407-8.

Gerlinger M, Rowan AJ, Horswell Set al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med. 2012;366(10):883-92.

Larkin J, Goh XY, Vetter M, et al. Epigenetic regulation in RCC: opportunities for therapeutic intervention. Nat Rev Urol. 2012 Jan 17;9(3):147-55.

Dr Amit Bahl

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Consultant Oncologist with special interest in Urological Cancers (Prostate, Bladder, Renal, Penile) and Breast Cancers.

Recent publications

Hallam S, Govindarajulu S, Huckett B, Bahl A. Clin Oncol (R Coll Radiol). BRCA1/2 Mutation-associated Breast Cancer, Wide Local Excision and Radiotherapy or Unilateral Mastectomy: A Systematic Review. 2015 Sep;27(9):527-35

Bahl A, Masson S, Malik Z, et al. Final quality of life and safety data for patients with metastatic castration-resistant prostate cancer treated with cabazitaxel in the UK Early Access Programme (EAP) (NCT01254279). BJU Int. 2015 Jan 30. doi: 10.1111/bju.13069

Bahl A, Masson S, Malik Z, et al. Final Quality of Life and Safety Data for patients with mCRPC treated with Cabazitaxel in the UK Early Access Programme (NCT01254279). BJU Int. 2015 Jan 30. doi: 10.1111/bju.13069.

Rodriguez-Vida A, Bianchini D, Van Hemelrijck M, et al. Is there an antiandrogen withdrawal syndrome with enzalutamide? BJU Int. 2015 Mar;115(3):373-80.

Zielinska HA, Bahl A, Holly JM, Perks CM. Epithelial-to-mesenchymal transition in breast cancer: a role for insulin-like growth factor I and insulin-like growth factor-binding protein 3? Breast Cancer (Dove Med Press). 2015 Jan 19;7:9-19.

8 COMPETING INTERESTS OF AUTHORS

None.

9 TIMETABLE/MILESTONES

Send progress report to NETSCC, HTA – 28th February 2017

Submit assessment report to NETSCC, HTA – 28th March 2017

The timetable is based on an 11-month working time-frame, commencing in May 2016 assuming that the final approval of the protocol has been received by this time.

10 APPENDICES

Appendix 10.1. Draft search strategies

Clinical draft search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present.

1. Carcinoma, Renal Cell/
2. (renal cell carcinoma$ or cell renal carcinoma$ or renal carcinoma$ or kidney carcinoma$ or kidney cell carcinoma$ or renal adenocarcinoma$ or kidney adenocarcinoma$ or adenocarcinoma$renal or adenocarcinoma$kidney$).mp.
3. (hypernephroma$ or nephroid carcinoma$ or hypernephroid carcinoma$ or kidney hypernephroma$ or kidney pelvic carcinoma$ or kidney pyelocarcinoma$ or renal hypernephroma$ or grawitz tumo?r$ or renal cell neoplasm$ or renal cell cancer$ or renal tumo?r$ or carcinoma chromophobe cell kidney$ or chromophobe cell kidney carcinoma$).mp.
4. kidney neoplasms/
5. (cancer$ adj2 kidney$1).ti,ab.
6. (neoplasm$1 adj2 kidney$1).ti,ab.
7. (neoplasm$1 adj2 renal).ti,ab.
8. (cancer$ adj2 renal).ti,ab.
9. (tumo?r$1 adj2 kidney$1).ti,ab.
10. (tumo?r$1 adj2 renal).ti,ab.
11. or/1-10
12. (axitinib or inlyta or AG013736 or "AG 013736").mp.
13. (sorafenib or nexavar or bay 43-9006 or bay 439006 or bay43-9006 or bay439006).mp.
14. (sunitinib or sutent or pha 2909040ad or pha2909040ad or "su 010398" or "su 011248" or su 10398 or su10398 or su 11248 or su010398 or su011248 or su11248).mp.

15. (everolimus or afinitor or certican or zortress or nvp-rad-001 or rad-001 or rad 001a or rad001 or rad001a or sdz rad).mp.
16. (nivolumab or opdivo or ONO4538 or ONO 4538 or BMS936558 or BMS 936558 or MDX1106 or MDX 1106).mp.
17. (temsirolimus or cci-779 or cell-cycle-inhibitor-779 or nsc 683864 or nsc683864 or torisel).mp.
18. (bevacizumab or avastin or nsc 704865 or nsc704865 or anti-vegf or rhumab-vegf).mp.
19. (alpha-interferon or alfaferone or alferon or alpha ferone or cilferon or ginterferon or interferon-alpha or intropa or kemron or leukinferon or leukinferron or leukocyte interferon or refecon a or referon a3 or sumiferon or sumipheron or veldona).mp.
20. (armala or pazopanib or gw786034 or gw 786034 or sb 710468 or sb710468 or votrient).mp.
21. (biotest or bioleukin or interleukin-ii or 'interleukin-2 or il-2 or il2 or ro-236019 or tcgf or tsf).mp.
22. or/12-21
23. Randomized Controlled Trials as Topic/
24. randomized controlled trial/
25. Random Allocation/
26. Double Blind Method/
27. Single Blind Method/
28. clinical trial/
29. clinical trial, phase i.pt.
30. clinical trial, phase ii.pt.
31. clinical trial, phase iii.pt.
32. clinical trial, phase iv.pt.
33. controlled clinical trial.pt.
34. randomized controlled trial.pt.
35. multicenter study.pt.
36. clinical trial.pt.
37. exp Clinical Trials as topic/
38. (clinical adj trial$).tw.
39. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
40. PLACEBOS/
41. placebo$.tw.
42. randomly allocated.tw.
43. (allocated adj2 random$).tw.
44. or/23-43
45. case report.tw.
46. letter/
47. historical article/
48. or/45-47
49. 44 not 48
50. 11 and 22 and 49
51. Animals/ not Humans/
52. 50 not 51
53. (editorial or letter).pt.
54. 52 not 53

Health economics draft search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present.

1. exp Carcinoma, Renal Cell/ or (metastatic renal cell carcinoma or mrcc).ab,ti.
2. kidney metastas$.ab,ti.

3. renal cell neoplasm.ab,ti.
4. renal carcinoma.ab,ti.
5. (renal cell cancer or renal cancer$).ab,ti.
6. renal cell carcinoma.ab,ti.
7. exp Neoplasm Metastasis/ or metastas$.ab,ti.
8. exp kidney/ or (renal or kidney).ab,ti.
9. or/1-8
10. (axitinib or ag013736 or inlyta).ti.
11. (tivozanib or av-951).ti.
12. (pazopanib or armala or gw786034 or sb710468).ti.
13. (alpha-interferon or alfaferone or alferon or alpha ferone or cilferon or ginterferon or interferon-alpha or intropa or kemron or leukinferon or leukinferron or leukocyte interferon or refecon a or referon a3 or sumiferon or sumipheron or veldona).tw.
14. interleukin$.ti.
15. (sunitinib or sutent or pha 2909040ad or pha2909040ad or "su 010398" or "su 011248" or su 10398 or su10398 or su 11248 or su010398 or su011248 or su11248).ti.
16. (biotest or bioleukin or interleukin-ii or interleukin-2 or il-2 or il2 or ro-236019 or tcgf or tsf).ti. ()
17. (sorafenib bay 43-9006 or bay 439006 or bay43-9006 or bay439006 or nexavar).ti.
18. (everolimus or afinitor or certican or nvp-rad-001 or rad-001 or rad 001a or rad001 or rad001a or sdz rad).ti.
19. (temsirolimus or cci-779 or cell-cycle-inhibitor-779 or nsc 683864 or nsc683864 or torisel).ti.
20. (bevacizumab or avastin or nsc 704865 or nsc704865 or anti-vegf or rhumab-vegf).ti.
21. (nivolumab or opdivo or ONO4538 or ONO 4538 or BMS936558 or BMS 936558 or MDX1106 or MDX 1106).mp.
22. or/10-21
23. 9 and 22
24. animal/
25. 23 not 24
26. economics/
27. exp costs/ and cost analysis/
28. 28 exp economics, hospital/
29. economics, medical/
30. economics, pharmaceutical/
31. (economic$ or pharmaeconomic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
32. (cost or costs or costly or costing or costed).ti.
33. value for money.ti.
34. cost utility/
35. cost effectiveness/
36. or/26-35
37. limit 36 to yr=2006-2015
38. 25 and 37
39. 25 and 36
40. 9 and 38
41. cost utility
42. cost-utility/
43. cost$ utilit$/
44. cost$ benefit$/
45. 44 and 36
46. 44 or 36
47. exp Quality-Adjusted Life Years/
48. (Quality-adjusted life year$ or QALY$).mp.
49. 47 and 36
50. incremental cost effectiveness ratio/

51. icer/
52. (incremental cost effectiveness ratio or icer).mp.
53. 52 and 36
54. 36 or 47
55. limit 54 to yr=2006-2015
56. 25 and 55
57. 25 and 54
58. exp economics, hospital/
59. 53 and 58
60. 54 or 58
61. limit 60 to yr=2006-2015
62. 25 and 61
63. 25 and 60
64. 36 or 48
65. 64 or 58
66. limit 65 to yr=2006-2015
67. 25 and 66
68. 25 and 65
69. 9 and 65
70. limit 69 to yr=2006-2015

Appendix 10.2 Data extraction form: clinical effectiveness studies

Study or trial name (if none then use first author surname and date):			**Publication source (first author surname and year)**
Full reference for all publications (and summary of data extracted if more than one publication) :			
Design			
Study design			
Number of centres & Country/countries			
Recruitment dates			
Length of follow-up			
Source of funding			
Eligibility criteria (inclusion and exclusion)			
Participants and	**Intervention:**	**Comparator:**	

Study or trial name (if none then use first author surname and date):			**Publication source (first author surname and year)**
treatment arms			
Intervention, method of delivery, dose and frequency			
Concomitant medication(s) or therapies			
Cross-over or post-study interventions allowed (including number of patients)			
Number of cycles, dose reductions			
Treatment duration (and the data cut offs for each publication for the study)			
Number randomised			
Number who received study medication			
Number withdrawn/ discontinued and reasons			
Disease stage (advanced?) and/or metastatic disease			
Previous systemic therapy treatments, n (%)			
Age, years: mean±SD (range)			
Ethnicity, n (%)			
Male, n (%)			
Performance status (e.g. ECOG,MSKCC, Heng)			
Reported subgroups			
Reported outcomes			
Primary outcome			
Secondary outcomes			
Outcomes and time points with data reported for subgroups of prior baseline therapies			
Outcomes and time points with data reported for subgroups of baseline prognostic scores (e.g. ECOG, MSKCC)			
Results	**Intervention**	**Comparator**	**Publication and time since study start**

Study or trial name (if none then use first author surname and date):			**Publication source (first author surname and year)**
			(weeks/months)
PFS			
HR (95% CI)			
HR (95% CI) for subgroups based on prior therapy			
PFS mean ± SD (median [range]) months			
PFS mean ± SD (median [range]), months for subgroups based on prior therapy			
Number of progression events n(%)			
Overall survival			
HR, (95% CI)			
HR, (95% CI) for subgroups based on prior therapy			
Number of deaths, n(%)			
Number of deaths, n(%) for subgroups based on prior therapy			
Response			
Objective response rate, n (%)			
Complete response, rate n (%)			
Partial response rate, n (%)			
Stable disease, n (%)			
Time to response, months mean ± SD (median [range])			
Duration of response, months mean ± SD (median [range])			
Other measures of response			
HRQoL			
HRQoL (EQ-5D or SF-36 or other generic tool) baseline score mean ± SD (median [range])			

Study or trial name (if none then use first author surname and date):			**Publication source (first author surname and year)**
HRQoL change from baseline mean ± SD (median [range])			
Other HRQoL data			
Adverse events (AE's) Grade ≥3, n (%)			
Total AE's Grade ≥3			
Total AE's (any Grade)			
Adverse events (please add rows for each adverse event reported):			
Risk of bias			
	Risk assessment (low risk, high risk, unclear risk)	**Comments**	
Random sequence generation			
Allocation concealment			
Blinding (who [participants, personnel], and method)			
Other biases			
Progression-free survival			
-Blinding of outcome assessment			
-Incomplete outcome data			
-Selective reporting			
Overall survival			
-Blinding of outcome assessment			
-Incomplete outcome data			
-Selective reporting			
Response (partial response, disease stabilisation, progressive disease)			
-Blinding of outcome assessment			
-Incomplete outcome data			
-Selective reporting			
HRQoL			
-Blinding of outcome assessment			
-Incomplete outcome data			
-Selective reporting			
Adverse events			
-Blinding of outcome			

Study or trial name (if none then use first author surname and date):			Publication source (first author surname and year)
assessment			
-Incomplete outcome data			
-Selective reporting			
Abbreviations used in table: BSC, best supportive care; CI, confidence interval; n, number of patients; mRCC, metastatic renal cell carcinoma; NA, not applicable; NR, not reported; PFS, progression-free survival; RCC, renal cell carcinoma; RCT, randomised controlled trial; SD, standard deviation;			

Appendix 10.3 Health economic evaluation study quality assessment

NICE reference case[11]

Attribute	Reference case	Reviewer's comments
Decision problem	The scope developed by NICE	
Comparator(s)	Alternative therapies routinely used in the NHS	
Perspective costs	NHS and Personal Social Services	
Perspective benefits	All health effects on individuals	
Form of economic evaluation	Cost-utility analysis	
Time horizon	Sufficient to capture differences in costs and outcomes	
Synthesis of evidence on outcomes	Systematic review	
Outcome measure	QALYs	
Health states for QALY	Described using a standardised and validated instrument	
Benefit valuation	Time-trade off or standard gamble	
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	
Discount rate	An annual rate of 3.5% on both costs and health effects	
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	
Sensitivity analysis	Probabilistic sensitivity analysis	
Abbreviations used in table: NICE, National Institute for Health and Clinical Excellence; NHS, National Health Service; QALY, quality adjusted life year.		

Philips checklist[14]

Dimension of quality	Reviewers comments
Structure	
S1 Statement of decision problem/objective	

Dimension of quality	Reviewers comments
S2 Statement of scope/perspective	
S3 Rationale for structure	
S4 Structural assumptions	
S5 Strategies/comparators	
S6 Model type	
S7 Time horizon	
S8 Disease states/pathways	
S9 Cycle length	
Data	
D1 Data identification	
D2 Premodel data analysis	
D2a Baseline data	
D2b Treatment effects	
D2d Quality of life weights (utilities)	
D3 Data incorporation	
D4 Assessment of uncertainty	
D4a Methodological	
D4b Structural	
D4c Heterogeneity	
D4d Parameter	
Consistency	
C1 Internal consistency	
C2 External consistency	

Appendix 10.4 Team members' contributions

Steve Edwards, Head of Clinical & Economic Evidence, will act as the third reviewer for assessment of cost-effectiveness studies, validate data extraction and any data analysis required, validate the economic model, contribute to writing/editing of the report, be overall lead of the project and act as guarantor of the report.

Victoria Wakefield, Senior HTA Analyst, will act as co-reviewer for assessing trials on clinical effectiveness for inclusion and data extraction, conduct analyses as required and contribute to the writing/editing of the report.

Dr George Osei-Assibey, HTA Analyst, will act as co-reviewer for assessing trials on clinical effectiveness for inclusion and data extraction, and contribute to the writing/editing of the report.

Dr Charlotta Karner, HTA Analysis Manager, will act as the third reviewer for assessment of clinical-effectiveness trials, validate data extraction and any data analysis required, validate any analyses and contribute to writing/editing of the report.

Andrea Berardi, Health Economics Manager, will act as co-reviewer of the cost-effectiveness studies, develop the economic model, and contribute to the writing/editing of the report.

Mariana Bacelar, Senior Health Economist, will act as co-reviewer of the cost-effectiveness studies, develop the economic model, and contribute to the writing/editing of the report.

Fatima Salih, Health Economist, will act as co-reviewer of the cost-effectiveness studies, and contribute to the writing/editing of the report.

Clinical Expert Advisors, will provide clinical advice throughout the protocol development and review processes, and peer review drafts of the report.

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