Treatments for renal cell carcinoma [ID6186]

Final Analysis Plan

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1 Project Title

Treatments for renal cell carcinoma

2 Objectives

This project aims to capitalise on the efficiencies of assessing multiple technologies in a disease pathway and inform robust access decisions by building an evolving core model for a disease area. This will involve the following steps:

- Development of a platform model encompassing each decision node in the disease area and underpinning evidence syntheses, for advanced renal cell carcinoma from the first line of systemic treatment onwards
- Piloting NICE's pathways approach for evaluating technologies using the platform model; in this case renal cell carcinoma
- Understand the value in using observational evidence to characterise the treatment pathway, natural history, and patient characteristics
- Incorporate a user interface to the model during the final phase of the project.

This pilot has multiple objectives:

- To appraise the clinical and cost effectiveness of upcoming novel technologies for renal cell carcinoma (RCC)
- To pilot a modified approach to current Technology Appraisal processes, which involves the development of an open-source decision model which can be reused in future appraisals
- To understand the value in using observational evidence to characterise the treatment pathway, natural history of the condition, and patient characteristics
- To explore feasibility of considering alternative decision-making frameworks in complex multi-comparator and multi-line treatment pathways, as part of an exploratory secondary phase of work outside of formal appraisal processes if these decision-making frameworks are proposed

NICE selected RCC as the first pilot topic because of the expected pipeline of treatments. Additionally, RCC is a disease area that incorporates multi-comparator decision spaces, with dynamic decision making based on exposure to prior therapies, providing potential to effectively pilot and learn from the pathways process.

NICE is considering using the platform model for a later phase of exploratory work to consider how to make its guidance more timely, actionable and useable for the NHS.

To achieve these objectives the evaluation will be split into 5 phases. The first three phases will occur within the context of the initial evaluation based upon the platform model:

- Phase 1 – Scoping and preparatory work;
- Phase 2 – Academic evidence synthesis and modelling work; and
- Phase 3 – Evaluation and decision-making

The final two phases will occur outside of the evaluation context and as a later phase of exploratory work:

- Phase 4 – Incorporation of user interface; and
- Phase 5 – consideration of how the platform model could be used for alternative decision making frameworks

2.1 The role of open source modelling

At present, recommendations for each treatment in the pathway may have been informed by different NICE committees, making decisions across multiple access routes, and based on different decision-models with different structures, inputs and implementations.

A more advantageous solution would be to develop a high quality disease model to be used across all technology appraisals in that space. Moreover, if the disease model is developed and maintained in an open-source environment, it would be available to all relevant stakeholders without restriction in a way that would encourage collaborative development.

An attractive model for this type of approach is the Innovation and Value Initiative's Open-Source Value Project (IVI; Jansen et al. 2019[1]). Since the project began in

2018, IVI has developed three disease models – one in rheumatoid arthritis, one in non-small-cell lung cancer and one in major depressive disorder – that are made freely available to all users, with full open-source code posted in a public repository (GitHub).[2] As part of their development process, IVI holds regular public consultation seeking feedback on the structure and parameterisation of its analyses, and exposing their implementation to unrestricted scrutiny.

2.2 Rationale for the Phase 5 exploratory analysis exploring alternative decision frameworks to investigate the impact of sequencing

NICE often receives enquiries about how guidance for a technology fits within the broader pathway and relates to other available treatments, and how guidance applies in different clinical situations. The development of a platform model for a disease area would need to consider the breadth of treatments within that pathway. At a later phase within this project, after decision making for initial treatments using the platform model, NICE plans to test the feasibility of exploring the impact of sequencing if this is a reasonable approach following policy based research.

To facilitate the implementation of possible future decision frameworks within the multi-comparator space, the following outcomes are required to be assessed within the cost-effectiveness model:

- the mean net benefit associated within each option;
- the probability of each technology and/or sequence under consideration being the optimal solution;
- the expected opportunity losses that would accompany a decision to recommend a treatment or sequence.

Additional analyses may also be required, for example sensitivity analyses varying the willingness to pay (WTP) threshold used in calculation of net benefit, and the calculation of value of information (VoI) statistics from the expected opportunity loss.

3 Decision problem

Within this section information on the decision problem for the full RCC platform model is provided as well as information specific to the initial use case of the model: the appraisal of cabozantinib plus nivolumab in untreated advanced or metastatic renal cell carcinoma.

3.1 Background

RCC is a cancer that usually originates in the lining of the tubules of the kidney (the smallest tubes inside the nephrons) that help filter the blood and make urine. RCC is the most common type of kidney cancer, accounting for more than 80% of cases.[3] There are several types of RCC. The main ones are clear cell (accounting for around 75% of cases), papillary and chromophobe.[3]

Treatment depends on the location and stage of the cancer.[4] There are different staging systems for renal cell carcinoma, including the number system. It looks at the number and size of kidney tumours. The number system has four stages:

- Stage 1 and 2 (early stage where tumour is localised to the kidney)
- Stage 3 (locally advanced stage with possible spread to regional lymph nodes)
- Stage 4 (advanced, metastatic stage where tumour has spread beyond regional lymph nodes to other parts of the body).

In 2018, 9,438 new kidney cancer cases were diagnosed in England.[5] Of those, 40.2% had stage 1 disease, 7.6% had stage 2 disease, 15.5% had stage 3 disease and 20.5% had stage 4 disease.[4] The 5-year survival was 86.8%, 76.6%, 74.2% and 12.4% for stage 1, 2, 3, and stage 4 disease, respectively.[6]

3.2 Interventions

One intervention is to be appraised by NICE using the platform model during this project:

- Cabozantinib with nivolumab (Ipsen) for untreated advanced or metastatic renal cell carcinoma

Cabozantinib is a multiple receptor TKI and nivolumab is a PD-1 inhibitor. The combination received a positive opinion by the European Medicines Agency (EMA) in February 2021 for the first-line treatment of advanced renal cell carcinoma on the basis of the CheckMate 9ER Phase III trial.[7] The marketing authorisation holder for cabozantinib is Ipsen Pharma. The marketing authorisation holder for nivolumab is Bristol-Myers Squibb Pharma EEIG.

Cabozantinib is administered orally at a dose of 40 mg once daily. Nivolumab is given intravenously at a dose of either 240 mg every 2 weeks or 480mg every 4 weeks: the former was used in CheckMate 9ER while, based upon initial expert consultation, the latter is more likely to be used in clinical practice. In line with the trial, the Summary of Product Characteristics (SmPC) specifies that Cabozantinib "should be continued until disease progression or unacceptable toxicity. Nivolumab should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression" (p.3).[8]

In March 2021,[7] results from a median follow-up of 18.1 months in Checkmate showed that treatment with cabozantinib and nivolumab resulted in a median progression-free survival (PFS) of 16.6 months (95% confidence interval [CI], 12.5 to 24.9) compared to 8.3 months (95% CI, 7.0 to 9.7) for treatment with sunitinib alone (hazard ratio [HR] for disease progression or death, 0.51; 95% CI, 0.41 to 0.64; p<0.001). The probability of overall survival (OS) at 12-months was 85.7% (95% CI, 81.3 to 89.1) with cabozantinib and nivolumab and 75.6% (95% CI, 70.5 to 80.0) with sunitinib (HR for death, 0.60; 98.89% CI, 0.40 to 0.89; P = 0.001).

The final analysis from CheckMate 9ER reported in July 2022[9] (data cut-off of June 24, 2021) with a median follow-up of 32.9 months [IQR 30.4–35.9]). Median OS was 37.7 months (95% CI 35.5–not estimable) in the cabozantinib and nivolumab group and 34.3 months (95% CI 29.0–not estimable) in the sunitinib group (HR 0.70 [95% CI 0.55–0.90], p=0.0043). Median PFS was 16.6 months (95% CI 12.8–19.8) in the cabozantinib and nivolumab group versus 8.3 months (95% CI 7.0–9.7; HR 0.56 [95% CI 0.46−0.68], p<0.0001).

Belzutifan was originally scoped to be included in the pathway appraisal but will not be included in the final scope. NICE and the company are continuing to liaise about scheduling for this topic and further participation in the pathway evaluations.

3.3 The RCC treatment pathway

The treatment pathway for RCC can be divided into interconnected decision points based on the disease staging system and line of therapy (

Figure **1** and

Figure **2**). The focus of this project will be the treatment pathway for advanced stage RCC (

Figure **2**). Consideration will, however, be given to the restriction to treatment options available for advanced disease after pembrolizumab in the adjuvant setting for people at increased risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions.

Figure 1: Treatment pathway for early stage to locally advanced RCC

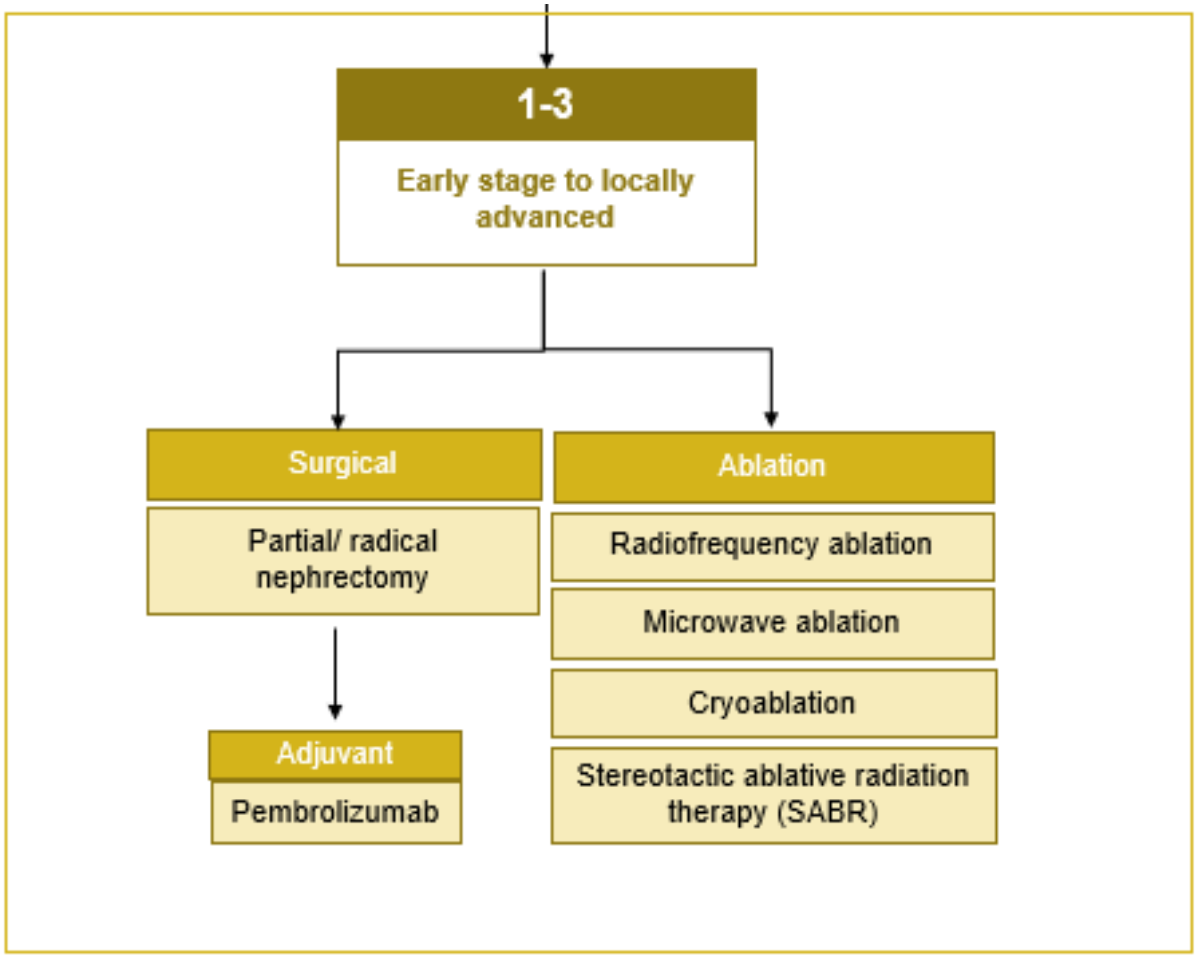
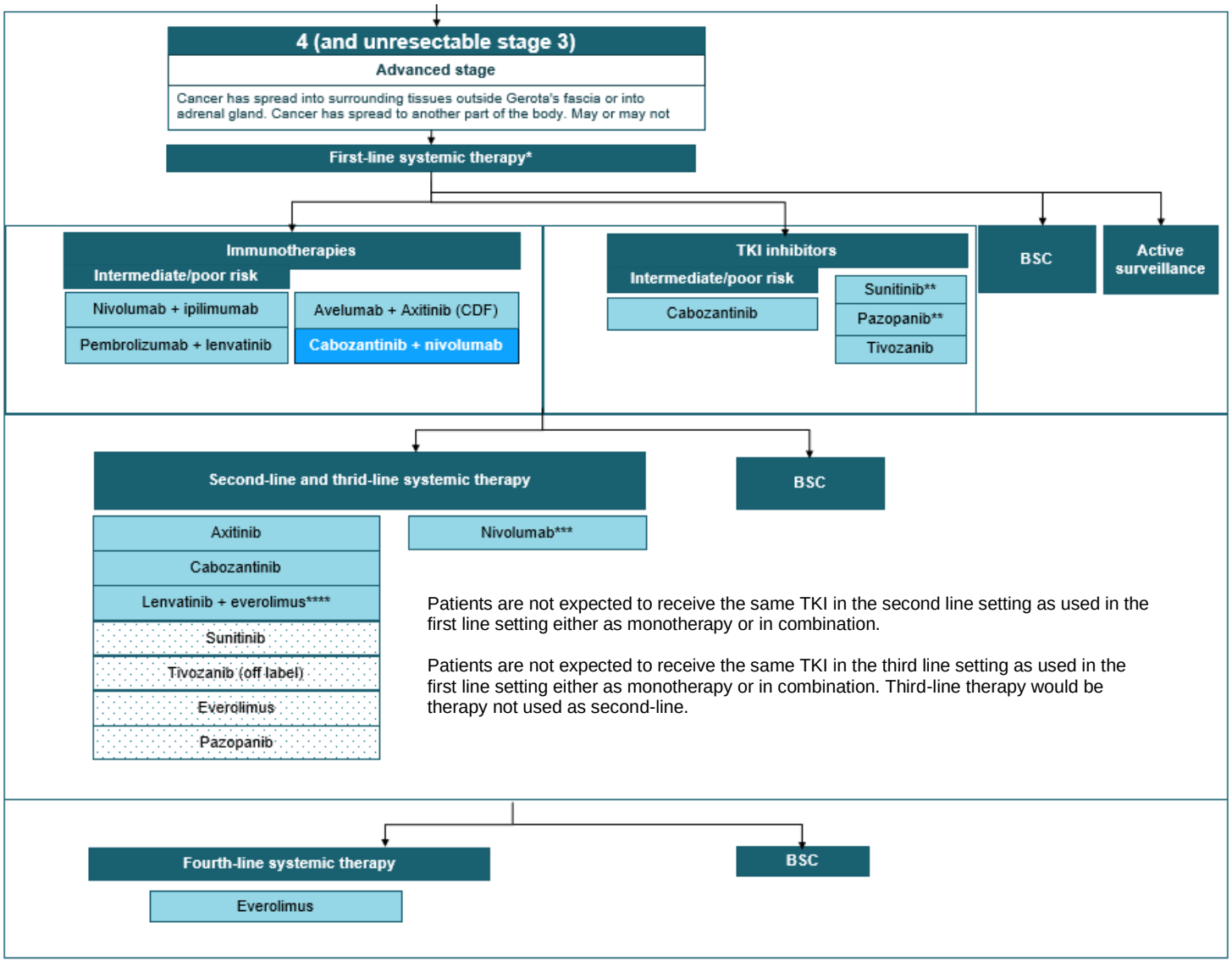


Figure 2: Treatment pathway for advanced stage RCC



Notes: * Patients can only receive treatment with a PD1 / PD-L1 inhibitor if they have not received a prior PD1 / PD-L1 inhibitor in the advanced setting and have not received a prior PD1 / PD-L1 inhibitor within the last 12 months in the adjuvant / neo-adjuvant setting

** Considered potential alternatives to PD-1 inhibitor-based combination therapy in IMDC favourable-risk disease(ESMO guideline recommendations; 2021) *** Nivolumab can only be used if the patient has not been previously treated with a mAb either in the advanced setting or less than 12 months prior in the adjuvant / neo-adjuvant setting

**** Lenvantinib + everolimus is only licensed for use after one prior anti-VEGF

3.3.1 Untreated advanced RCC

Current treatment options for untreated advanced RCC include:

- Immunotherapy combination therapy:
  - For people with intermediate or poor-risk cancer as defined by the International Metastatic RCC Database Consortium (IMDC), NICE recommends nivolumab plus ipilimumab (a PD-1 inhibitor with a CTLA-4 inhibitor; TA780) and pembrolizumab plus lenvatinib (a TKI with a PD-1/PD-L1 inhibitor; TA858)
  - For the broader population, avelumab with axitinib is available via the Cancer Drugs Fund (a PD-1/PD-L1 inhibitor with a TKI, TA645)
- TKI monotherapy: sunitinib, pazopanib or tivozanib as recommended by NICE technology appraisal guidance (TA169, TA215 and TA512) and cabozantinib (TA542 which is only recommended for patients with intermediate or poor-risk cancer)

The British Medical Journal (BMJ) RCC best practice guidelines (July, 2022)[10] recommend a similar approach to NICE, though with some variation. Preferred treatment options were either pembrolizumab with axitinib (not recommended by NICE), nivolumab with cabozantinib (under evaluation within this analysis), pembrolizumab with lenvatinib, or nivolumab with ipilimumab. Secondary options included avelumab with axitinib, and sunitinib, pazopanib and cabozantinib. Avelumab with axitinib was considered secondary treatment on the basis that a benefit for OS compared to other treatments had not been demonstrated.[11] TKI monotherapies were considered to be the preferred option for patients who cannot receive or tolerate immune checkpoint inhibition, while tivozanib was considered a tertiary option.

The European Society for Medical Oncology (ESMO) guideline recommendations (2021) align with those specified by the BMJ with exception that monotherapy TKIs sunitinib or pazopanib were considered potential alternatives to PD-1 inhibitor-based combination therapy in IMDC favourable-risk disease. This was due to a lack of clear superiority for PD-1-based combinations over sunitinib in this subgroup of patients.

3.3.2 Previously treated advanced RCC

As the approach to treatment of metastatic RCC has changed with the approval of immune checkpoint inhibitors as first-line therapy, there is considerable uncertainty surrounding the optimum treatment pathway for previously treated RCC, and there are limited data on the efficacy of subsequent therapies following use of immune checkpoint inhibitors.[10]

Current treatment options include:

- Axitinib (following either a cytokine or tyrosine kinase inhibitor; TA333)
- Cabozantinib (following a VEGF-targeted therapy; TA463)
- Lenvatinib plus everolimus (following one prior VEGF-targeted therapy for patients with ECOG 0-1; TA498)
- Nivolumab (for patients with have not previously had a PD-1/PD-L1 inhibitor; TA417)
- Everolimus (following a VEGF-targeted therapy TA432; this is understood to be used primarily at fourth line)
- A first line TKI (sunitinib, pazopanib or tivozanib) following nivolumab plus ipilimumab

ESMO guideline recommendations are to give a VEGFR that has not previously been given.[12] They note that: “Robust prospective second-line data exclusively after first-line PD-1 inhibitor-based combination therapy are lacking. Prospective datasets exist for axitinib, pazopanib and sunitinib, but they include mixed patient populations and small numbers. There are also retrospective, exploratory, subset analyses … Responses were seen (~20%) in all of these studies and outcome was in line with the expectations for sequencing therapy … It is likely that sequencing different targeted therapies approved in advanced RCC is beneficial, as was the case in the pre-ICI era. Rechallenge with ICIs is unproven, and should not be regarded as a standard option” (p.1512 – 1514).

While the BMJ recommendations for previously treated RCC include options not currently recommended in the UK (e.g., aldesleukin, bevacizumab plus interferon alfa, temsirolimus and sorafenib) their broad recommendations are consistent with the above approach.

3.4 Population and relevant sub-groups

The relevant population for evaluation of clinical and cost-effectiveness varies per appraisal. For nivolumab plus cabozantinib the relevant population is people with untreated advanced or metastatic renal cell carcinoma.

The scope for this appraisal is for people with advanced or metastatic RCC. Although systemic treatments are mostly suitable for those with metastatic disease (Stage 4), they may be offered to people with locally advanced (Stage 3) disease where this is unresectable. Due to this, people with Stage 4 RCC or Stage 3 unresectable RCC will be included.

In this appraisal, subgroup analyses of treatment effects will be conducted according to IMDC risk score.[13,14] This scoring system predicts survival in people with metastatic RCC treated with systemic therapy based on time from diagnosis, karnofsky performance status, and laboratory measures of hemoglobin, corrected calcium and neutrophils. Within the current treatment pathway RCC, some treatments are only recommended for people with IMDC poor or intermediate risk status (Section 3.3).

Where feasible, subgroup analyses will also be conducted according to prior treatment (or treatment class) received.

3.5 Comparators

The relevant comparators in the NICE scope for the current phase of this appraisal are shown in Table 1. In addition to these treatments active surveillance is listed as a comparator in the final NICE scope. This is not included within the EAG analysis plan as a treatment of interest as it is considered to happen prior to the decision node at which this model starts. Clinical advice received is that clinical decision making first involves deciding whether or not a patient would benefit from any kind of systemic therapy and then, once clinicians and patients agree therapy should be initiated, a choice is made between available treatment options.

Table 1: Comparators

Comparators to cabozantinib plus nivolumab
• Pazopanib • Tivozanib • Sunitinib • Cabozantinib (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Nivolumab plus ipilimumab (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Pembrolizumab plus lenvatinib (only for intermediate- or poor-risk disease as defined in the IMDC criteria)

3.6 Outcomes

Outcome measures will include:

- overall survival (OS)
- progression-free survival (PFS)
- time to next treatment
- time on treatment
- response rates
- duration of response
- adverse effects (AEs) of treatment
- health-related quality of life (HRQoL)

4 Clinical effectiveness methods

The review of clinical effectiveness evidence will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination.

4.1 Search strategy

Two separate searches and selection processes will be conducted (a systematic search to identify clinical effectiveness evidence and a targeted search to identify real-world evidence [RWE]).

4.1.1 Systematic search for clinical effectiveness evidence

Our search for clinical effectiveness evidence will unfold in two stages. First, we will search for published systematic reviews and meta-analyses of treatments for

advanced RCC, focusing on systematic reviews published since 2020. From these, we will identify relevant RCTs for inclusion from a selection of the most recent, comprehensive SLRs. Second, we will undertake top-up searches for randomised trials to address gaps in these reviews. This may include searches for trials published since the search dates of included SLRs, or for trials on interventions not covered in any SLRs. In all cases, searches will include terms for disease terms and terms for the relevant study designs.

Searches for systematic reviews will be undertaken in MEDLINE, Embase, Cochrane Database of Systematic Reviews and The International Network of Agencies for Health Technology Assessment (INAHTA), using the search strategy outlined in Appendix 1. Relevant NICE technology appraisals will be identified by handsearching the NICE website and will be screened for further relevant studies. Top-up searches for trials will include MEDLINE, Embase, CENTRAL (Cochrane Central Register of Controlled Trials) and trial registers (WHO ICTRP and clinicaltrials.gov). In addition, top-up searches for RCTs will include forward citation searches of trials identified in existing SLRs to identify later data cuts, including in conference abstracts (e.g. using trial names, author names) and the relevant NICE technology appraisals will be consulted to identify unpublished data previously provided to NICE.

4.1.2 Targeted search for observational evidence to characterise the treatment pathway, natural history and patient characteristics

In line with the recommendations in the NICE RWE framework,[15] a targeted search will be conducted to identify observational evidence to characterise the treatment pathway, the natural history of the disease and patient characteristics. This is described in detail in Appendix 3. The potential uses for this evidence are listed below. In each case we would consider information for both the whole patient population and according to IMDC risk score subgroups:

- Understand current treatment pathways (sequences) being used
- Assess the generalisability of trial data based on demographic and disease-related characteristics (particularly prognostic variables)
- Improve long-term extrapolations (particularly for historical therapies)
- Inform baseline risk (either as scenario analysis or base case)

- Understand the difference between trial-based assessment of progression and intermediate disease-related outcomes recording in practice
- Inform doses used in practice for treatments where dose adjustments can be applied & understand the proportion of planned doses that are missed
- Look at how HRQoL changes over time (dependent on collection of such data)
- Inform healthcare resource utilisation (HCRU) and costs per health state (dependent on collection of such data)
- Fill in data gaps for later lines for any comparators which have not been studied in trials (this is not expected to be required)
- Explore the impact of sequencing on effectiveness (this is considered unlikely to be possible)

4.2 Study selection

Selection criteria for studies of clinical effectiveness and for observational studies are described in 4.2.1 and 4.2.2 respectively.

4.2.1 Selection of clinical effectiveness evidence

In the first round of screening, we will include a) systematic reviews of RCTs b) of pharmacological treatments for advanced renal cell carcinoma c) published since 2020. We will exclude reviews focusing on radiotherapy or surgical interventions. We will identify the highest-quality and broadest systematic reviews to identify relevant randomised trials and map these trials against comparators and lines of treatment to identify any gaps.

In top-up searches (to update and fill gaps in the systematic review evidence), we will include a) randomised trials b) of pharmacological treatments used within the treatment pathway following the disease to treat with systemic treatments (pazopanib, tivozanib, sunitinib, cabozantinib, nivolumab plus ipilimumab, lenvatinib plus pembrolizumab, axitinib, lenvatinib plus everolimus, everolimus, cabozantinib with nivolumab, nivolumab, avelumab plus axitinib, best supportive care) c) for patients with advanced renal cell carcinoma d) reporting at least one outcome from overall survival, progression-free survival, time to next treatment, time to discontinuation, response rates, adverse effects of treatment, health-related quality of life.

Further details on these inclusion/exclusion criteria are described in Table 2.

Table 2: Inclusion and exclusion criteria for clinical effectiveness evidence

PICOS item	Include	Exclude
Population	Studies of participants with advanced (unresectable Stage 3 or Stage 4) renal cell carcinoma at any treatment line	Studies of participants with early stage (not advanced) renal cell carcinoma
Intervention	Round 1 (systematic reviews): any pharmacological treatment for advanced renal cell carcinoma used in the systemic setting Round 2 (RCTs and extensions of RCTs): cabozantinib plus nivolumab, pazopanib, tivozanib, sunitinib, cabozantinib, nivolumab plus ipilimumab, lenvatinib plus pembrolizumab, axitinib, lenvatinib plus everolimus, everolimus, nivolumab, avelumab plus axitinib*	Any other treatments not listed under inclusion Treatments used in the adjuvant setting
Comparator	Any of the other interventions listed above (i.e. head-to-head studies) Dose comparison studies Usual care / physicians' choice / BSC	Non-pharmacological treatments only
Outcomes	Studies reporting at least one outcome from: • OS • PFS • time to next treatment • time on treatment • response rates • duration of response • AEs of treatment¥ • HRQoL	Studies not reporting an included outcome

Study design	Round 1: systematic reviews of RCTs published since 2020 Round 2: RCTs. Conference abstracts will be included unless data are superseded by another conference abstract or full journal article	Round 1: systematic reviews that did not contain RCTs, systematic reviews of treatment effect modifiers. Round 2: non-randomised trials, observational studies, case reports, editorials and commentaries

Abbreviations: AE, adverse events; BSC, best supportive care; HRQoL, health-related quality of life; OS, overall survival, PFS, progression-free survival; RCT, randomised controlled trials

Notes: * as belzutifan was included within the NICE draft scope it was included within the search terms for the searches conducted, these studies will, however, not be included during screening ¥ we will extract data for Grade 3+ treatment-emergent adverse events and the total number of treatment-emergent adverse events leading to discontinuation. Additional lower grade adverse events of interest may be extracted following clinical advice

4.2.2 Selection of observational evidence to characterise the treatment pathway, natural history and patient characteristics

Prospective and retrospective studies of people with advanced RCC based in the United Kingdom and focusing on describing the treatment pathway, natural history of disease or patient characteristics of people with renal cell carcinoma will be included. Further details are provided in **Table 3**. More details of the real-world data search are provided in Appendix 3. Additional details on relevant UK sources identified (such as RCC registries) will be sought by the EAG via email contact with the lead authors of relevant publications. The EAG will also extract publicly available data from resource such as the National Cancer Registration and Analysis Service (NCRAS). Finally, it is possible that the NICE team will gain and share access to data generated specifically for this project via a healthcare data analytics company.

Table 3: Inclusion and exclusion criteria for observational evidence

PICOS item	Include	Exclude
Population	Studies including participants with advanced renal cell carcinoma	Studies limited to participants with early stage (not advanced) renal cell carcinoma
Outcomes	Studies primarily describing one of the following: Treatment pathways Natural history of disease Patient characteristics	Studies not reporting an included outcome
Study design	Cohort studies enrolling participants prospectively, or using routinely	Case reports, editorials and commentaries

	collected data to construct retrospective cohorts	
Location	Studies based in any region of the United Kingdom	Studies based outside of the United Kingdom

4.3 Study selection process

To identify both clinical effectiveness studies (systematic reviews and top-up studies) and observational studies (to characterise the treatment pathway, natural history and patient characteristics), the abstracts and titles of references retrieved by the electronic searches will be screened for relevance against the criteria specified above (**Table 2** for clinical effectiveness and **Table 3** for observational studies). Full paper copies of potentially relevant studies will be obtained. The retrieved articles will be independently assessed for inclusion by two reviewers using the pre-specified inclusion/exclusion criteria. Discrepancies will be resolved by discussion, with involvement of a third reviewer, where necessary. All duplicate papers will be double checked and excluded.

4.4 Data extraction and quality appraisal

4.4.1 Data extraction

Included clinical effectiveness studies (identified via systematic reviews and top-up searches) and included observational studies will be extracted by one reviewer into a bespoke database and checked by a second reviewer. The data extraction grid is provided in Appendix 2. Discrepancies will be resolved by discussion, with the involvement of a third reviewer if necessary. For time to event outcomes, we will extract both summary hazard ratios from the last data cut and, where necessary, digitise curves using standard methods (e.g. the Guyot algorithm), assuming censoring linearly across time intervals.

In cases where there are missing data in the published or submitted clinical effectiveness studies, attempts will be made to contact authors. This will only be done where data for an entire key outcome, Kaplan-Meier data for a key outcome or sub-group data (baseline characteristics or outcomes) are missing. A deadline for

response to the initial contact of 4 weeks will be imposed. Additional time might be allowed should the author be able to supply the data requested.

4.4.2 Quality appraisal

For both clinical effectiveness and observational studies, individual study quality will be assessed by one reviewer and checked by a second reviewer. Any disagreement will be resolved by consensus and if necessary, a third reviewer will arbitrate.

Randomised trials will be assessed using the standardised criteria for evaluating evidence quality as recommended by NICE for submissions to its HTA programme. For observational studies, a relevant checklist will be used relevant to the study design. For example, ROBINS-I will be used to appraise the quality of non-randomised cohort studies. In addition, for RWE identified from external datasets, such as patient registries, NICE's Data Suitability Assessment Tool (DataSAT) will be completed to provide structured information on data suitability including provenance, quality and relevance.[15] These criteria will be considered when conducting quality appraisal.

4.5 Synthesis

Identified systematic reviews will be tabulated as an appendix without any further synthesis.

Randomised trials will be synthesised using appropriate meta-analysis methods. Evidence networks for each outcome will be formed by decision point on the pathway (i.e. line of treatment or class of prior treatment), combining decision points 3 and 4 (second and third line RCC) if need be due to similar comparator sets.

Feasibility of network meta-analyses (NMAs) will be considered by examining distribution of likely effect modifiers (e.g. age, sex, regional distribution of patient population, disease characteristics, subsequent therapies and adjustment for cross-over for OS) over networks.

NMAs will be carried out where evidence is sufficient for time-to-event outcomes (PFS, time-on-treatment, time to next treatment, OS) and two measures of AE

(treatment emergent G3+ and treatment emergent AEs leading to discontinuation). NMAs will not be carried out for response, HRQoL or individual AEs.

Continuous and binary outcomes will further be grouped with respect to similarity of follow-up times and combined using standardised mean differences or odds ratios as appropriate. Time to event outcomes will be analysed using two strategies: one exploratory and one primary. The exploratory strategy, for all time-to-event outcomes, will rely on hazard ratios from longest follow-up combined after log transformation using an inverse variance method.

The primary strategy, which will focus on progression-free survival as a priority outcome (with time to next treatment and time to treatment discontinuation as second-stage outcomes if data are available, but not OS), will use a parametric modelling method.

As a first strategy, we will use fractional polynomial analyses as, based on previous appraisals in RCC, it is expected that there may be issues in justifying proportional hazards for all endpoints. These will draw on grouped data in time intervals of one week (coincident with the model cycle length), or aggregated to four weeks as appropriate, to estimate survivor functions arising from arms in included trials. Where possible, we will draw on data in their original form (requested as grouped survival data), digitising curves using the standard Guyot algorithm where all other attempts to access grouped data have failed. Model selection will compare second-order polynomials drawn from the set of powers defined by −2, −1, −0.5, 0, 0.5, 1, 2, 3 as standard[16].

Model selection will begin with frequentist fixed effects models, identifying a candidate set of ‘most likely’ models on the basis of visual fit to observed data, clinical plausibility including elicited landmark survival estimates and biological considerations and statistical fit using Akaike Information Criterion (AIC) [17]

A Bayesian analysis of selected models will be carried out introducing random effects. Random effects will only be considered on the basis of ‘time-invariant’ heterogeneity, that is only using between-study variance on intercept terms.[16] The general framework will be to use random effects in a Bayesian framework with Markov chain Monte Carlo estimation, including informative priors from Turner (2015)

if available and appropriate and vague or weakly informative priors otherwise. Estimation will use two chains of 100,000 iterations with 20,000 iterations discarded as burn-in. Bayesian model comparisons will use Deviance Information Criterion (DIC). Convergence will be assessed using standard methods, including autocorrelation and Brooks-Gelman-Rubin diagnostic plots. Inconsistency will be assessed for each network using DIC estimates.

If the fractional polynomial method generates inappropriate or clinically implausible results, estimates from each trial will be meta-analysed using a multivariate strategy[18] (i.e. allowing two-dimensional treatment effects) drawing on parametric distributions (e.g. Weibull, log-normal, log-logistic). The most appropriate distribution will be chosen for each network on the basis of visual fit across included trials, DIC scores and clinical plausibility of projections against landmark survival (e.g. five years).

It is considered unlikely that overall-survival data will be identified for untreated patients with a pathway in line with UK practice due to the predominance of the use of more than one line of immune oncology within trials in the literature. Synthesis of overall-survival data using methods accounting for time-varying hazards will only be conducted if sufficient data is identified either without such issues or with adjustment conducted for subsequent therapy use outside of UK practice. A basic meta-analysis of hazard ratios will instead be conducted and used for validation of the economic model rather than direct model input.

5 Cost effectiveness methods

5.1 Identification of existing evidence

A comprehensive search of the health economic literature will be undertaken to identify existing economic evaluations of the interventions and competitors listed within the NICE scope and to identify studies reporting quality of life data in the form of utilities.

5.1.1 Search strategies

The same inclusion and exclusion criteria will be applied for the economic searches as for the clinical searches in respect of patient population. The same criteria will be applied for intervention and comparators for searches for economic evaluations. No

intervention or comparator limits will be applied to studies reporting quality of life data in the form of utilities or cost and resource use evidence.

Searches will be limited to 2009 onwards (aligning with the publication of the first NICE appraisal in RCC) for economic evidence and utilities, and from 2017 onwards for cost and resource use data to ensure that only relevant data is found (aligning with the entry of immune-oncology options into clinical practice post TA417).

Table 4 provides the full PICOS design for each of the 3 searches.

Table 4: Inclusion and exclusion criteria for cost effectiveness studies

PICOS item	Include	Exclude
Population	Studies of participants with advanced (stage 3 unresectable and stage 4) RCC	Studies of participants with early stage (not advanced) RCC
Intervention (economic evaluation searches only)	Nivolumab plus cabozantinib, pazopanib, tivozanib, sunitinib, cabozantinib, nivolumab plus ipilimumab, lenvatinib plus pembrolizumab, axitinib, lenvatinib plus everolimus, everolimus, nivolumab, avelumab plus axitinib*	Any other treatments not listed under inclusion Treatments used in the adjuvant setting
Comparator (economic evaluation searches only)	Any of the other interventions listed above (i.e. head-to-head studies) Usual care / physicians' choice / best supportive care	Any other treatments
Outcomes	**Economic evaluations** Incremental Cost Effectiveness Ratio expressed as cost per life year gained or cost per QALY Cost savings (cost-minimisation studies only) **Utility studies** Quality of life data expressed in the form of utilities regardless of the method of elicitation and valuation **Cost and resource use studies** Resource use data from UK studies Cost data from UK studies	Studies not reporting an included outcome
Study design	Economic evaluations (cost-effectiveness, cost-benefit, cost-consequence or cost-minimisation)	Abstracts with insufficient methodological details Editorials and commentaries

	Systematic reviews of economic evaluations or utilities Conference abstracts will be included unless data are superseded by another conference abstract or full journal article	
Data limits	Economic evaluations: 2009 Utility studies: 2009 Cost and resource use studies: 2017	

Abbreviations: QALY, quality-adjusted life year; RCC, renal cell carcinoma

Notes: * as belzutifan was included within the NICE draft scope it was included within the search terms for the searches conducted, these studies will, however, not be included during screening

Searches will be undertaken in Medline and Embase (using a health economics filter), INAHTA, ScHARRHUD, CEA Registry, RePEc and EQ-5D; searches for pre 2015 material will be carried out in NHS EED.

5.1.2 Study selection process

Abstracts and titles of references retrieved by the electronic searches will be screened for relevance against the criteria specified above (**Table 4**). Full paper copies of potentially relevant studies will be obtained. The retrieved articles will be independently assessed for inclusion by two reviewers using the pre-specified inclusion/exclusion criteria. Discrepancies will be resolved by discussion, with involvement of a third reviewer, where necessary. All duplicate papers will be double checked and excluded.

Dependent upon the volume of articles included as part of full text screening data extraction may be limited to a prioritised list of articles. Prioritisation criteria may include:

- Country for economic evaluations (prioritising UK and then European and Western studies)
- Language (prioritising to studies in English)
- Date (prioritising to more recent studies within a treatment line)

5.1.3 Data extraction and quality appraisal

Included studies will be extracted by one reviewer into a bespoke database and checked by a second reviewer. Discrepancies will be resolved by discussion, with the involvement of a third reviewer if necessary.

A data extraction sheet is provided in Appendix 2. Reviewers will extract relevant information on model structure, time horizon, perspective of the analysis, primary source of effectiveness data, resource use and costs, utility information and the conclusions and any key limitations of the analysis highlighted within the study.

In cases where there are missing data or unclear reporting in the published or submitted utility studies, attempts will be made to contact authors. This will only be done where data for an entire key outcome or sub-group data (baseline characteristics or outcomes) are missing. A deadline for response to the initial contact of 4 weeks will be imposed. Additional time might be allowed should the author be able to supply the data requested.

Methods and findings from included economic evaluations will be summarised in a tabular format and synthesised in a narrative review. Economic evaluations carried out from the perspective of the UK NHS and Personal Social Services (PSS) perspective will be presented in greater detail. If sufficient EQ-5D data are found during the searches for utility data, the EAG will restrict the data extraction to EQ-5D data.

The quality of individual studies will be assessed by one reviewer and checked by a second reviewer. Any disagreement will be resolved by consensus and if necessary a third reviewer will arbitrate.

Critical appraisal will be undertaken using the following tools:

- Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 checklist for economic evaluations.[19]
- The Philips 2004 checklist for decision analytical models.[20]
- The AMSTAR checklist for systematic reviews.[21]

5.2 Economic modelling

A *de novo* economic model will be built to allow the assessment of the nivolumab plus cabozantinib for patients with untreated advanced RCC.

The economic model will be built with this appraisal in mind; in addition to the expansion to future appraisals within RCC and expansion for use as a template for other cancers.

5.2.1 Software

The model will be built in R and is intended to be made open-access using 'GitHub' to improve replicability and collaboration. The model will be built broadly aligning with good practice guidelines, for example, the ZIN guidelines for building models in R.[22]

Underlying data (model inputs) will not need to be publicly available and can be shared confidentially with NICE abiding to the principles for handling confidential information outlined in the HTE manual .The publicly available version of the economic model will use dummy data in the correct format as inputs where data is marked as either academic or commercial in confidence within the original data source. The dummy data will be created using the methods used to redact an Excel model as part of a NICE submission.

Data which are expected to need to be marked as confidential and redacted to reduce the potential for back-calculation of confidential prices include:

- PAS price discounts
- Any individual patient level data provided by the company
- Time on treatment input data
- Relative dose intensity input data
- Market share data for subsequent therapies
- Reported ICERs (PAS price and list price)

Redaction will only be required after receipt of the company evidence submission as data included prior to this will be publicly available.

5.2.2 Structure

A state transition model structure is expected to be utilised given the need to look at multiple decision nodes within a treatment pathway and the requirements to produce the exploratory analyses required for Phase 4. The option to explore the impact of a partitioned survival structure upon the analysis is also expected to be incorporated in line with the recommendations within NICE TSD 19.[23] All structural assumptions will be documented and accompanying rationales provided. Clinical expert opinion will be sought to determine the appropriate model structure. The model will be built in a flexible manner to allow the exploration of key structural uncertainties where needed and possible.

Health states will be descriptive of the patient's current health, relevant history, quality of life, and resource utilisation patterns. Within the model design phase, consideration will be given to whether PFS (commonly collected in trials as a measure of health status but less commonly available in real-world datasets) or an alternative measure such as time to next treatment or time to discontinuation provides the most suitable representation.

5.2.3 Time horizon and cycle length

The time horizon for the economic analysis will be long enough to reflect any differences in costs or outcomes between the technologies under comparison. A weekly cycle length will be applied to account for the difference in dosing regimens across treatments. Half cycle correction will not be applied given the short cycle length.

5.2.4 Model inputs

Model inputs will come from the previously described systematic reviews; real-world evidence identified either via the targeted review described or provided by the healthcare data analytics company and data provided by companies within their submissions. In cases where parameters required to populate the model are not available from published studies or company submissions, expert clinical opinion will be considered. It is expected that an expert elicitation exercise will be undertaken to inform expectations around long-term survival given the lack of data to support

estimates following recent changes to the RCC pathway. Materials from the STEER repository[24,25] which was developed in line with the MRC protocol, will be used to conduct this exercise.

The model will initially be built using publicly available data with in-confidence data supplied by companies and real-world evidence inputs incorporated into the model at a later stage using a standardised input template. It is expected that the model built using publicly available data will be essentially a 'proof of concept.' Given the timeframes available, this means that some R code modules may not yet be available at this stage. Additionally, the results are not expected to hold face validity at this stage (not least due to the fact that company trial data will not have been included).

The model will initially focus on the evaluation of whether nivolumab plus cabozantinib is cost-effective in a first line position. This will require the determination of the most cost-effective treatment in that placement within the pathway given the current and expected mix of subsequent therapies following the new treatment being introduced.

The effect of treatment will be modelled via the indirect comparison described in Section 4.5. Consideration will be given to the duration of the treatment effect with the option included within the model to explore the potential impact of treatment effect waning (via either imposition of equal hazards between treatments at a set time point or a linear change in hazards towards the reference treatment between two timepoints).

As appropriate, cost data will be obtained from NHS reference costs, Unit Costs of Health and Social Care, eMit, BNF, published sources such as previous technology appraisals or data submitted by companies during this project. Costs will consist of direct medical costs (e.g. drug costs and cost of adverse events, monitoring and administering treatment) and direct non-medical costs (e.g. healthcare professional costs). Resource use and costs will be valued from the NHS and Personal Social Services perspective. Both costs and outcomes will be discounted at 3.5% per annum after the first year in accordance with the NICE methods guide.[26]

5.2.5 Model outputs

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 life year gained (LYG), net monetary benefit and net health benefit. Base case analyses will be probabilistic as this generates expected outcomes and costs and is in line with the NICE manual.[26] Additional scenario and one-way sensitivity analyses will be conducted where they add value and clarity.

Within Phase 4 of the project, the health economic model will be embedded into an interactive web browser using R-Shiny functionality to provide an easy-to-understand user-interface. This is intended to test the use of such functionality to support the development, critique and understanding of the model structure (and underlying R code) for decision makers and other stakeholders in future models.

5.2.6 Validation and calibration

Initially model outputs will be compared to the data used as model inputs (for example visual comparison to Kaplan Meier data), to ensure the appropriateness of model structure and data derivation. The model will then be compared to the projections from other models previously used for NICE STAs in the same decision node. Dependent on what data are available from the review of RWD sources these data may either be used as a direct model input or within the validation exercise.

Clinical expert input will be used to ensure that the model retains clinical face validity.

Given the proposed primary model structure (state transition), calibration to expected OS estimates may be required. If this is the case, we would propose to conduct this within a likelihood-based framework.

6 Company submissions

Company submissions received by the assessment group before the submission deadline specified by NICE will be appraised. Anything submitted after the deadline will only be considered if this has been agreed by NICE.

Company submissions are expected to be limited to the provision of clinical effectiveness data with narrative, provision of data for input to the economic model

and supply of comments on the proposed model structure. Company comments on the model structure will be responded to individually using the same table format as is used for the factual inaccuracy step.

Any academic or commercial in confidence data taken from a company submission will be underlined and highlighted as appropriate in the report.

A confidential appendix will be supplied to NICE in which ICERs including all of the relevant commercial arrangements are presented.

7 Competing interests of authors

None.

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Appendix 1 Draft search strategies

Clinical effectiveness searches

Ovid MEDLINE(R) ALL <1946 to December 19, 2022>

#	Search terms	hits
1	exp renal cell carcinoma/	38967
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	79433
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	50496
4	or/1-3	85754
5	exp Kidney Neoplasms/co, dt, pc, th [Complications, Drug Therapy, Prevention & Control, Therapy]	24002
6	exp antineoplastic agents/	1224683
7	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ti.	2918163
8	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ab. /freq=2	4058024
9	exp nivolumab/	4780
10	(nivolumab or "anti-PD-1 human monoclonal antibody MDX-1106" or "Opdivo" or "Opdivo Injection" or "NIVO" or "BMS-936558" or "MDX-1106" or "ONO-4538").mp.	9104
11	exp Ipilimumab/	2762
12	(ipilimumab or "anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody" or "MOAB CTLA-4" or "monoclonal antibody CTLA-4" or Yervoy or "MDX-CTLA-4" or "BMS-734016" or "MDX-010").mp.	5188
13	(pembrolizumab or keytruda or "MK-3475" or "SCH 900475").mp.	8075
14	(lenvatinib or kisplyx or E7080 or "E?7080").mp.	1797
15	(avelumab or bavencio or MSB0010718 or "MSB?0010718C").mp.	847
16	exp axitinib/	689
17	(axitinib or Inlyta or "AG-013736").mp.	1402
18	(cabozantinib or cometriq or cabometyx or XL184).mp.	1459
19	exp sunitinib/	4073
20	(sunitinib or Sutent or "SU11248" or "SU011248" or "SU11248").mp.	7243
21	(pazopanib or Votrient or "GW786034B").mp.	2218
22	(tivozanib or Fotivda or AV951 or "AV?951").mp.	150
23	exp everolimus/	5540

24	(everolimus or Zortress or Certican or Afinitor or Votubia or "RAD 001" or RAD001 or SDZ-RAD or SDZRAD or SDZ RAD).mp.	8786
25	(Belzutifan or Welireg or MK-6482 or PT2977).mp.	53
26	or/5-25	6153895
27	(systematic review or meta-analysis).pt.	294997
28	meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/	332150
29	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.	296051
30	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.	14743
31	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.	36779
32	(data synthes* or data extraction* or data abstraction*).ti,ab,kf.	37881
33	(handsearch* or hand search*).ti,ab,kf.	10835
34	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.	33973
35	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.	11663
36	(meta regression* or metaregression*).ti,ab,kf.	13549
37	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	438050
38	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	319211
39	(cochrane or (health adj2 technology assessment) or evidence report).jw.	21080
40	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf.	16821
41	(outcomes research or relative effectiveness).ti,ab,kf.	10926
42	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.	4168
43	(meta-analysis or systematic review).mp.	410085
44	(multi* adj3 treatment adj3 comparison*).ti,ab,kf.	285
45	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.	177
46	umbrella review*.ti,ab,kf.	1226
47	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	13
48	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.	18
49	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	11
50	or/27-49	644080
51	("Case Reports" or Comment or Editorial or "Historical article" or Letter).pt. or "case report".ti.	4587898
52	4 and 26 and 50	1486
53	52 not 51	1394
54	limit 53 to yr="2018 -Current"	628

Database: Embase <1974 to 2022 December 19>

#	Search terms	hits
1	exp renal cell carcinoma/	31174
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	114211
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	77252
4	or/1-3	128712
5	exp kidney cancer/dm, dt, si, th [Disease Management, Drug Therapy, Side Effect, Therapy]	28575
6	exp antineoplastic agent/	2638818
7	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ti.	3623259
8	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ab. /freq=2	6000219
9	exp nivolumab/ (32745)	32745
10	(nivolumab or "anti-PD-1 human monoclonal antibody MDX-1106" or "Opdivo" or "Opdivo Injection" or "NIVO" or "BMS-936558" or "MDX-1106" or "ONO-4538").mp.	34448
11	exp Ipilimumab/	21936
12	(ipilimumab or "anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody" or "MOAB CTLA-4" or "monoclonal antibody CTLA-4" or Yervoy or "MDX-CTLA-4" or "BMS-734016" or "MDX-010").mp.	22838
13	exp pembrolizumab/	31244
14	(pembrolizumab or keytruda or "MK-3475" or "SCH 900475").mp.	32860
15	exp lenvatinib/	5387
16	(lenvatinib or kisplyx or E7080 or "E?7080").mp.	5629
17	exp avelumab/	5280
18	(avelumab or bavencio or MSB0010718 or "MSB?0010718C").mp.	5482
19	exp axitinib/ (6639)	6639
20	(axitinib or Inlyta or "AG-013736").mp.	6844
21	exp cabozantinib/	6024
22	(cabozantinib or cometriq or cabometyx or XL184).mp.	6307
23	exp sunitinib/	26404
24	(sunitinib or Sutent or "SU11248" or "SU011248" or "SU11248").mp.	27267
25	exp pazopanib/	10059
26	(pazopanib or Votrient or "GW786034B").mp.	10323
27	exp tivozanib/	782
28	(tivozanib or Fotivda or AV951 or "AV?951").mp.	814
29	exp everolimus/	31492
30	(everolimus or Zortress or Certican or Afinitor or Votubia or "RAD 001" or RAD001 or SDZ-RAD or SDZRAD or SDZ RAD).mp.	35736
31	exp belzutifan/	144
32	(Belzutifan or Welireg or MK-6482 or PT2977).mp.	173

33	or/5-32	8690322
34	meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/	576741
35	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.	362049
36	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.	17188
37	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.	51879
38	(data synthes* or data extraction* or data abstraction*).ti,ab,kf.	46313
39	(handsearch* or hand search*).ti,ab,kf.	13182
40	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.	44792
41	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.	18756
42	(meta regression* or metaregression*).ti,ab,kf.	16660
43	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	687084
44	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	415676
45	(cochrane or (health adj2 technology assessment) or evidence report).jw.	29538
46	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf.	24545
47	(outcomes research or relative effectiveness).ti,ab,kf.	15635
48	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.	7108
49	(meta-analysis or systematic review).mp.	649107
50	(multi* adj3 treatment adj3 comparison*).ti,ab,kf.	410
51	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.	256
52	umbrella review*.ti,ab,kf.	1294
53	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	27
54	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.	19
55	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	22
56	or/34-55	926571
57	("Case Reports" or Comment or Editorial or "Historical article" or Letter).pt. or "case report".ti.	2348064
58	4 and 33 and 56	3089
59	58 not 57	2999
60	limit 59 to yr="2018 -Current"	1550
61	"Conference Abstract".pt.	4623992
62	60 not 61	1153

The Cochrane Library

#1 MeSH descriptor: [Carcinoma, Renal Cell] explode all trees 1064
#2 ((renal or kidney) NEAR/3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)):ti,ab 4049
#3 ("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma"):ti,ab 3634
#4 #1 or #2 or #3 4674
#5 MeSH descriptor: [Antineoplastic Agents] explode all trees 13346
#6 (efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic):ti,ab 1171199
#7 MeSH descriptor: [Nivolumab] explode all trees 615
#8 (nivolumab or "anti-PD-1 human monoclonal antibody MDX-1106" or "Opdivo" or "Opdivo Injection" or "NIVO" or "BMS-936558" or "MDX-1106" or "ONO-4538") 2650
#9 MeSH descriptor: [Ipilimumab] explode all trees 278
#10 (ipilimumab or "anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody" or "MOAB CTLA-4" or "monoclonal antibody CTLA-4" or Yervoy or "MDX-CTLA-4" or "BMS-734016" or "MDX-010") 1692
#11 (pembrolizumab or keytruda or "MK-3475" or "SCH 900475") 2623
#12 (lenvatinib or kisplyx or E7080 or "E?7080") 535
#13 (avelumab or bavencio or MSB0010718 or "MSB?0010718C") 351
#14 MeSH descriptor: [Axitinib] explode all trees 112
#15 (axitinib or Inlyta or "AG-013736") 391
#16 (cabozantinib or cometriq or cabometyx or XL184) 475
#17 MeSH descriptor: [Sunitinib] explode all trees 353
#18 (sunitinib or Sutent or "SU11248" or "SU011248" or "SU11248") 1379
#19 (pazopanib or Votrient or "GW786034B") 626
#20 (tivozanib or Fotivda or AV951 or "AV?951") 85
#21 MeSH descriptor: [Everolimus] explode all trees 1645
#22 (everolimus or Zortress or Certican or Afinitor or Votubia or "RAD 001" or RAD001 or SDZ-RAD or SDZRAD or SDZ RAD) 4442
#23 (Belzutifan or Welireg or MK-6482 or PT2977) 26
#24 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 1173781
#25 #4 and #24 3904
[CDSR only – 21]

INAHTA

(((Belzutifan or Welireg or MK-6482 or PT2977)) OR ((everolimus or Zortress or Certican or Afinitor or Votubia or "RAD 001" or RAD001 or SDZ-RAD or SDZRAD or SDZ RAD)) OR ("Everolimus"[mhe]) OR ((tivozanib or Fotivda or AV951)) OR ((pazopanib or Votrient or "GW786034B")) OR ((sunitinib or Sutent or "SU11248" or "SU011248" or "SU11248")) OR ("Sunitinib"[mhe]) OR ((cabozantinib or cometriq or cabometyx or XL184)) OR ((axitinib or Inlyta or "AG-013736")) OR ("Axitinib"[mhe]) OR ((avelumab or bavencio or MSB0010718)) OR ((lenvatinib or kisplyx or E7080)) OR ((pembrolizumab or keytruda or "MK-3475" or "SCH 900475")) OR ((ipilimumab or "anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody" or "MOAB CTLA-4" or "monoclonal antibody CTLA-4" or Yervoy or "MDX-CTLA-4" or "BMS-734016" or "MDX-010")) OR ("Ipilimumab"[mhe]) OR ((nivolumab or "anti-PD-1

human monoclonal antibody MDX-1106" or "Opdivo" or "Opdivo Injection" or "NIVO" or "BMS-936558" or "MDX-1106" or "ONO-4538")) OR ("Nivolumab"[mhe]) OR ((efficacy or effectiveness or treatment or therapy or management or chemotherapy or adjuvant or antineoplastic)) OR ("Antineoplastic Agents"[mhe])) AND (("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear cell" or "non clear cell" or hypermephroma or "hypernephroid carcinoma")) OR ("Carcinoma, Renal Cell"[mhe]) OR (renal AND (carcinoma or cancer or tumor or tumour or neoplasm or adenocarcinoma)) OR ((kidney AND (carcinoma or cancer or tumor or tumour or neoplasm or adenocarcinoma))))

Utilities and economic studies searches

Search strategies: economic evaluations

Database(s): **Ovid MEDLINE(R) ALL** 1946 to January 09, 2023
Search Strategy:

#	Searches	Results
1	exp renal cell carcinoma/	39067
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	79756
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	50731
4	or/1-3	86085
5	(advanced or unresect* or un?resect* or nonresect* or (non adj2 resect*) or inopera* or unopera* or metastas* or metastat* or "end stage" or "late-stage" or "late stage" or terminal or "stage 3" or "stage iii" or "stage three" or "stage 4" or "stage iv" or "stage four").ti,ab.	1634422
6	4 and 5	31811
7	exp Kidney Neoplasms/co, dt, pc, th [Complications, Drug Therapy, Prevention & Control, Therapy]	24032
8	exp antineoplastic agents/	1226142
9	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ti.	2927184
10	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ab. /freq=2	4075456
11	exp nivolumab/	4822
12	(nivolumab or "anti-PD-1 human monoclonal antibody MDX-1106" or "Opdivo" or "Opdivo Injection" or "NIVO" or "BMS-936558" or "MDX-1106" or "ONO-4538").mp.	9197
13	exp Ipilimumab/	2772
14	(ipilimumab or "anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody" or "MOAB CTLA-4" or "monoclonal antibody CTLA-4" or Yervoy or "MDX-CTLA-4" or "BMS-734016" or "MDX-010").mp.	5215
15	(pembrolizumab or keytruda or "MK-3475" or "SCH 900475").mp.	8170
16	(lenvatinib or kisplyx or E7080 or "E?7080").mp.	1829
17	(avelumab or bavencio or MSB0010718 or "MSB?0010718C").mp.	861
18	exp axitinib/	691
19	(axitinib or Inlyta or "AG-013736").mp.	1414
20	(cabozantinib or cometriq or cabometyx or XL184).mp.	1474
21	exp sunitinib/	4077
22	(sunitinib or Sutent or "SU11248" or "SU011248" or "SU11248").mp.	7276
23	(pazopanib or Votrient or "GW786034B").mp.	2233

24	(tivozanib or Fotivda or AV951 or "AV?951").mp.	152
25	exp everolimus/	5549
26	(everolimus or Zortress or Certican or Afinitor or Votubia or "RAD 001" or RAD001 or SDZ-RAD or SDZRAD or SDZ RAD).mp.	8808
27	(Belzutifan or Welireg or MK-6482 or PT2977).mp.	55
28	or/7-27	6174505
29	Economics/	27484
30	"costs and cost analysis"/	51061
31	Cost allocation/	2017
32	Cost-benefit analysis/	91428
33	Cost control/	21659
34	Cost savings/	12669
35	Cost of illness/	31192
36	Cost sharing/	2713
37	"deductibles and coinsurance"/	1846
38	Medical savings accounts/	547
39	Health care costs/	43742
40	Direct service costs/	1217
41	Drug costs/	17301
42	Employer health costs/	1097
43	Hospital costs/	11907
44	Health expenditures/	23560
45	Capital expenditures/	2001
46	Value of life/	5797
47	exp economics, hospital/	25665
48	exp economics, medical/	14376
49	Economics, nursing/	4013
50	Economics, pharmaceutical/	3092
51	exp "fees and charges"/	31278
52	exp budgets/	14065
53	(low adj cost).mp.	82135
54	(high adj cost).mp.	18878
55	(health?care adj cost$).mp.	15660
56	(fiscal or funding or financial or finance).tw.	188804
57	(cost adj estimate$).mp.	2676
58	(cost adj variable).mp.	50
59	(unit adj cost$).mp.	3031
60	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	389987
61	or/29-60	897051
62	(editorial or letter or case report or clinical conference or review).pt.	4916431
63	exp "systematic review"/ or exp meta analysis/	296555
64	(systematic or meta* or "mixed treatment comparison" or "indirect treatment comparison").ti,ab.	3349855

65	62 not (63 or 64)	4302209
66	(6 and 28 and 61) not 65	305
67	limit 66 to yr="2009 -Current"	271

Database(s): **Embase** 1974 to 2023 January 09
Search Strategy:

#	Searches	Results
1	exp renal cell carcinoma/	31521
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	114590
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	77537
4	or/1-3	129231
5	(advanced or unresect* or un?resect* or nonresect* or (non adj2 resect*) or inopera* or unopera* or metastas* or metastat* or "end stage" or "late-stage" or "late stage" or terminal or "stage 3" or "stage iii" or "stage three" or "stage 4" or "stage iv" or "stage four").ti,ab.	2252114
6	4 and 5	51612
7	exp kidney cancer/dm, dt, si, th [Disease Management, Drug Therapy, Side Effect, Therapy]	28662
8	exp antineoplastic agent/	2648585
9	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ti.	3635889
10	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ab. /freq=2	6026332
11	exp nivolumab/	33112
12	(nivolumab or "anti-PD-1 human monoclonal antibody MDX-1106" or "Opdivo" or "Opdivo Injection" or "NIVO" or "BMS-936558" or "MDX-1106" or "ONO-4538").mp.	34839
13	exp Ipilimumab/	22138
14	(ipilimumab or "anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody" or "MOAB CTLA-4" or "monoclonal antibody CTLA-4" or Yervoy or "MDX-CTLA-4" or "BMS-734016" or "MDX-010").mp.	23050
15	exp pembrolizumab/	31637
16	(pembrolizumab or keytruda or "MK-3475" or "SCH 900475").mp.	33277
17	exp lenvatinib/	5462
18	(lenvatinib or kisplyx or E7080 or "E?7080").mp.	5707
19	exp avelumab/	5358
20	(avelumab or bavencio or MSB0010718 or "MSB?0010718C").mp.	5564
21	exp axitinib/	6691
22	(axitinib or Inlyta or "AG-013736").mp.	6897
23	exp cabozantinib/	6091
24	(cabozantinib or cometriq or cabometyx or XL184).mp.	6378

25	exp sunitinib/	26506
26	(sunitinib or Sutent or "SU11248" or "SU011248" or "SU11248").mp.	27375
27	exp pazopanib/	10114
28	(pazopanib or Votrient or "GW786034B").mp.	10378
29	exp tivozanib/	788
30	(tivozanib or Fotivda or AV951 or "AV?951").mp.	820
31	exp everolimus/	31601
32	(everolimus or Zortress or Certican or Afinitor or Votubia or "RAD 001" or RAD001 or SDZ-RAD or SDZRAD or SDZ RAD).mp.	35873
33	exp belzutifan/	146
34	(Belzutifan or Welireg or MK-6482 or PT2977).mp.	175
35	or/7-34	8723841
36	Socioeconomics/	157038
37	Cost benefit analysis/	92471
38	Cost effectiveness analysis/	174213
39	Cost of illness/	20913
40	Cost control/	74692
41	Economic aspect/	121653
42	Financial management/	119686
43	Health care cost/	217619
44	Health care financing/	13782
45	Health economics/	35027
46	Hospital cost/	24546
47	(fiscal or financial or finance or funding).tw.	271614
48	Cost minimization analysis/	3871
49	(cost adj estimate$).mp.	4050
50	(cost adj variable$).mp.	309
51	(unit adj cost$).mp.	5343
52	or/36-51	1077979
53	(chapter or "conference review" or editorial or erratum or letter or note or "case report" or methodology or "clinical protocol" or nonhuman or "short survey" or "practice guideline" or review).pt,ti.	7322646
54	exp "systematic review"/ or exp meta analysis/	509695
55	(systematic or meta* or "mixed treatment comparison" or "indirect treatment comparison").ti,ab.	4111380
56	53 not (54 or 55)	6435399
57	"conference abstract".pt.	4650391
58	("american association for cancer research" or aacr or "american society of clinical oncology" or asco or "american urological association" or aua or esmo or "european association of urology" or eau or "genitourinary cancers symposium" or "international conference on translational cancer medicine" or "international society for pharmacoeconomics and outcomes research" or ispor).nc.	316614
59	57 not 58	4334100

60	6 and 35 and 52	1067
61	60 not (56 or 59)	931
62	limit 61 to yr="2009 -Current"	866

Search strategies: utilities

Database(s): **Ovid MEDLINE(R) ALL** 1946 to January 09, 2023
Search Strategy:

#	Searches	Results
1	exp renal cell carcinoma/	39067
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	79756
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	50731
4	or/1-3	86085
5	(advanced or unresect* or un?resect* or nonresect* or (non adj2 resect*) or inopera* or unopera* or metastas* or metastat* or "end stage" or "late-stage" or "late stage" or terminal or "stage 3" or "stage iii" or "stage three" or "stage 4" or "stage iv" or "stage four").ti,ab.	1634422
6	4 and 5	31811
7	"Value of Life"/	5797
8	Quality of Life/	257015
9	quality of life.ti,kf.	110630
10	((instrument or instruments) adj3 quality of life).ab.	3834
11	Quality-Adjusted Life Years/	15318
12	quality adjusted life.ti,ab,kf.	16684
13	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf.	26843
14	disability adjusted life.ti,ab,kf.	4934
15	daly*.ti,ab,kf.	4456
16	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf.	29912
17	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kf.	2555
18	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf.	604
19	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf.	7393

20	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf.	39
21	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf.	448
22	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kf.	22951
23	(hye or hyes).ti,ab,kf.	76
24	(health* adj2 year* adj2 equivalent*).ti,ab,kf.	48
25	(pqol or qls).ti,ab,kf.	450
26	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf.	692
27	nottingham health profile*.ti,ab,kf.	1222
28	sickness impact profile.ti,ab,kf.	1091
29	exp health status indicators/	340260
30	(health adj3 (utilit* or status)).ti,ab,kf.	88742
31	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf.	15264
32	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf.	13811
33	disutilit*.ti,ab,kf.	593
34	rosser.ti,ab,kf.	107
35	willingness to pay.ti,ab,kf.	8121
36	standard gamble*.ti,ab,kf.	906
37	(time trade off or time tradeoff).ti,ab,kf.	1616
38	tto.ti,ab,kf.	1350
39	(hui or hui1 or hui2 or hui3).ti,ab,kf.	1892
40	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf.	21519
41	duke health profile.ti,ab,kf.	92
42	functional status questionnaire.ti,ab,kf.	129
43	dartmouth coop functional health assessment*.ti,ab,kf.	13
44	or/7-43	730445
45	6 and 44	659
46	(editorial or letter or case report or clinical conference or review).pt.	4916431
47	exp "systematic review"/ or exp meta analysis/	296555
48	(systematic or meta* or "mixed treatment comparison" or "indirect treatment comparison").ti,ab.	3349855
49	46 not (47 or 48)	4302209
50	45 not 49	632
51	exp animals/ not humans.sh.	5080261
52	50 not 51	630
53	limit 52 to yr="2009 -Current"	497

Database(s): **Embase** 1974 to 2023 January 09
Search Strategy:

#	Searches	Results
1	exp renal cell carcinoma/	31521
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	114590
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	77537
4	or/1-3	129231
5	(advanced or unresect* or un?resect* or nonresect* or (non adj2 resect*) or inopera* or unopera* or metastas* or metastat* or "end stage" or "late-stage" or "late stage" or terminal or "stage 3" or "stage iii" or "stage three" or "stage 4" or "stage iv" or "stage four").ti,ab.	2252114
6	4 and 5	51612
7	socioeconomics/	157038
8	exp Quality of Life/	615092
9	quality of life.ti,kf.	172098
10	((instrument or instruments) adj3 quality of life).ab.	5284
11	Quality-Adjusted Life Year/	33347
12	quality adjusted life.ti,ab,kf.	25354
13	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf.	42369
14	disability adjusted life.ti,ab,kf.	5901
15	daly*.ti,ab,kf.	5727
16	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf.	48537
17	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kf.	2848
18	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf.	993
19	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf.	11770
20	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf.	67
21	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf.	510
22	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kf.	37025
23	(hye or hyes).ti,ab,kf.	165
24	(health* adj2 year* adj2 equivalent*).ti,ab,kf.	55
25	(pqol or qls).ti,ab,kf.	730

26	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf.	859
27	nottingham health profile*.ti,ab,kf.	1645
28	nottingham health profile/	621
29	sickness impact profile.ti,ab,kf.	1279
30	sickness impact profile/	2372
31	health status indicator/	3400
32	(health adj3 (utilit* or status)).ti,ab,kf.	115941
33	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf.	24379
34	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf.	18145
35	disutilit*.ti,ab,kf.	1184
36	rosser.ti,ab,kf.	139
37	willingness to pay.ti,ab,kf.	12249
38	standard gamble*.ti,ab,kf.	1201
39	(time trade off or time tradeoff).ti,ab,kf.	2329
40	tto.ti,ab,kf.	2129
41	(hui or hui1 or hui2 or hui3).ti,ab,kf.	2960
42	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf.	35879
43	duke health profile.ti,ab,kf.	117
44	functional status questionnaire.ti,ab,kf.	169
45	dartmouth coop functional health assessment*.ti,ab,kf.	13
46	or/7-45	945003
47	6 and 46	1793
48	(chapter or "conference review" or editorial or erratum or letter or note or "case report" or methodology or "clinical protocol" or nonhuman or "short survey" or "practice guideline" or review).pt,ti.	7322646
49	exp "systematic review"/ or exp meta analysis/	509695
50	(systematic or meta* or "mixed treatment comparison" or "indirect treatment comparison").ti,ab.	4111380
51	48 not (49 or 50)	6435399
52	"conference abstract".pt.	4650391
53	("american association for cancer research" or aacr or "american society of clinical oncology" or asco or "american urological association" or aua or esmo or "european association of urology" or eau or "genitourinary cancers symposium" or "international conference on translational cancer medicine" or "international society for pharmacoeconomics and outcomes research" or ispor).nc.	316614
54	52 not 53	4334100
55	47 not (51 or 54)	1406
56	exp animal/ not human/	5197941
57	55 not 56	1400
58	limit 57 to yr="2009 -Current"	1173

Search strategies: GB costs

Database(s): **Ovid MEDLINE(R) ALL** 1946 to January 09, 2023
Search Strategy:

#	Searches	Results
1	exp renal cell carcinoma/	39067
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	79756
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	50731
4	or/1-3	86085
5	(advanced or unresect* or un?resect* or nonresect* or (non adj2 resect*) or inopera* or unopera* or metastas* or metastat* or "end stage" or "late-stage" or "late stage" or terminal or "stage 3" or "stage iii" or "stage three" or "stage 4" or "stage iv" or "stage four").ti,ab.	1634422
6	4 and 5	31811
7	(cost? adj2 (illness or disease or sickness)).tw.	4713
8	(burden? adj2 (illness or disease? or condition? or economic*)).tw.	52154
9	("quality-adjusted life years" or "quality adjusted life years" or QALY?).tw.	16193
10	Quality-adjusted life years/	15318
11	"cost of illness"/	31192
12	Health expenditures/	23560
13	(out-of-pocket adj2 (payment? or expenditure? or cost? or spending or expense?)).tw.	6449
14	(expenditure? adj3 (health or direct or indirect)).tw.	10563
15	((adjusted or quality-adjusted) adj2 year?).tw.	27647
16	or/7-15	137065
17	exp United Kingdom/	387636
18	(national health service* or nhs*).ti,ab,in.	259084
19	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.	47472
20	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.	2385721
21	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or	1690052

	chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.	
22	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.	67819
23	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.	249038
24	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.	32543
25	or/17-24	2994651
26	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp australia/ or exp oceania/) not (exp United Kingdom/ or europe/)	3272772
27	25 not 26	2836173
28	6 and 16 and 27	37
29	limit 28 to yr="2017 -Current"	20

Database(s): **Embase** 1974 to 2023 January 09
Search Strategy:

#	Searches	Results
1	exp renal cell carcinoma/	31521
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	114590

3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	77537
4	or/1-3	129231
5	(advanced or unresect* or un?resect* or nonresect* or (non adj2 resect*) or inopera* or unopera* or metastas* or metastat* or "end stage" or "late-stage" or "late stage" or terminal or "stage 3" or "stage iii" or "stage three" or "stage 4" or "stage iv" or "stage four").ti,ab.	2252114
6	4 and 5	51612
7	(cost? adj2 (illness or disease or sickness)).tw.	7424
8	(burden? adj2 (illness or disease? or condition? or economic*)).tw.	80797
9	("quality-adjusted life years" or "quality adjusted life years" or QALY?).tw.	28324
10	Quality-adjusted life years/	33347
11	"cost of illness"/	20913
12	exp "health care cost"/	329309
13	(out-of-pocket adj2 (payment? or expenditure? or cost? or spending or expense?)).tw.	9136
14	(expenditure? adj3 (health or direct or indirect)).tw.	13703
15	((adjusted or quality-adjusted) adj2 year?).tw.	39526
16	or/7-15	455004
17	exp United Kingdom/	454101
18	(national health service* or nhs*).ti,ab,in.	381803
19	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.	56714
20	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.	3527152
21	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or	2788284

	peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.	
22	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.	114720
23	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.	384034
24	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.	53264
25	or/17-24	4315463
26	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp australia/ or exp oceania/) not (exp United Kingdom/ or europe/)	3502186
27	25 not 26	4068006
28	6 and 16 and 27	150
29	limit 28 to yr="2017 -Current"	78

Search strategies: other databases, for general economic studies

INAHTA
((("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear cell" or "non clear cell" or hypermephroma or "hypernephroid carcinoma") OR ("Carcinoma, Renal Cell"[mhe]) OR (renal AND (carcinoma or cancer or tumor or tumour or neoplasm or adenocarcinoma)) OR ((kidney AND (carcinoma or cancer or tumor or tumour or neoplasm or adenocarcinoma))) AND (economic* OR cost*) FROM 2009 TO 2023
= 137 hits

ScHCARRHUD (all searches in “any field”)
"renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear cell" or "non clear cell" or hypermephroma or "hypernephroid carcinoma"
OR

renal AND (carcinoma or cancer or tumor or tumour or neoplasm or adenocarcinoma)
OR
kidney AND (carcinoma or cancer or tumor or tumour or neoplasm or adenocarcinoma)
= 8 hits

CEA Registry (utilities)
In Abstract. Renal cell cancer or renal cell carcinoma or kidney cancer or kidney carcinoma
= 201 utilities in 46 articles (saved as CSV file)

RePEc
Unable to find a way to export data

EQ-5D
Renal cell cancer or renal cell carcinoma or kidney cancer or kidney carcinoma
= 0 hits

NHS EED
"Renal cell cancer" or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma"
= 18 hits

Appendix 2 Data extraction grids

Clinical effectiveness search

Clinical%20data%20
extraction%20templ

Economic searches

Economic%20data%
20extraction%20tem

Observational data search

Data extraction grid will be produced at a later date.

Appendix 3 Choosing fit-for-purpose RWE data

The method chosen to identify fit for purpose RWE data has been informed by NICE's RWE framework* which states "We encourage developers to identify candidate data sources through a systematic, transparent and reproducible search where possible." The framework recommends the use of the Health Data Research UK Innovation Gateway.

In order to identify sources which may not yet be registered via the Gateway we will identify potential real-world evidence sources through a three-pronged search strategy, incorporating a search of the published literature, the Health Data Research UK Innovation Gateway, and a general web search:

1. **Medline and Embase**: Search results for observational studies in the UK on renal cell carcinoma will be uploaded into Endnote, followed by assessment of abstracts to identify any registry/RWE data sources used. Abstracts will be screened in Endnote. Search strategies listed below.
2. **Health Data Research UK Innovation Gateway**: Searches will include renal cell cancer, renal cell carcinoma, kidney cancer or kidney carcinoma. Results will be sifted on screen.
3. **Web search (Google and Bing)**: Search terms will include (renal cell cancer or renal cell carcinoma or kidney cancer or kidney carcinoma) AND (registry or real-world data or real-world evidence). These will be performed as a series of separate searches, given the limitations of web search platforms. The first 50 results of each search will be scanned and sifted on screen.

The criteria against which candidate sources will be assessed are:

- **Population**: renal cell carcinoma
- **Intervention**: medical therapy
- **Data collected**: OS, PFS, time on treatment, time to next treatment, HRQL, current treatment pathways (sequences) being used, prognostic variables, risk scores, health costs
- **Geography**: UK
- **Time**: collection of data has occurred since 2020

* NICE. NICE real-world evidence framework. Corporate document [ECD9]. Published: 23 June 2022 London: National Institute for Health and Care Excellence; 2022. Available from: https://www.nice.org.uk/corporate/ecd9/chapter/overview

Following initial assessment of search results using the Health Data Research UK Innovation Gateway, we have identified the following four registries as likely sources of relevant real-world evidence. Unfortunately, the data we would require from SACT, CPRD or HES for this project are not available in the public domain and cannot be accessed within the timescales of this project.

Registry name	Notes	Data availability	Action required
National Cancer Registration and Analysis Service (NCRAS)	Includes data from the Get Data Out programme, which publishes in-depth, anonymous data about cancer	Some data are freely available through the digital.nhs.uk website and the National Disease Registration service (NDRS)	None
Systemic Anti-Cancer Therapy (SACT) data set	Contains 44 data items which cover: patient and tumour characteristics, trust and consultant details, treatment characteristics including drug names and drug combinations (regimens), outcome fields.	Requires an N3/HSCN connection for full functionality	NICE to support access
Clinical Practice Research Datalink (CPRD)	CPRD collects anonymised patient data from a network of GP practices across the UK. Data are linked to a range of other health related data to provide a longitudinal, representative UK population health dataset. The data encompass 60 million patients, including 18 million currently registered patients.	Access to CPRD data, including UK Primary Care Data, and linked data such as Hospital Episode Statistics, is subject to protocol approval via CPRD's Research Data Governance (RDG) Process	NICE to support access
Hospital Episode Statistics (HES)	Hospital Episode Statistics (HES) is a database containing details of all admissions, A and E attendances and outpatient appointments at NHS hospitals in England.	All requests to access record-level data from NHS Digital are handled by the Data Access	NICE to support access

		Request Service (DARS).	

The following two registries may provide useful data, but we remain unsure as to whether they are still operational, accessible, or relevant to the PATT programme. We will therefore email lead authors of the articles that used the registries to enquire.

Registry name	Query	Action
RECCORD (Renal Cell Carcinoma Outcomes Research Dataset) registry	Is the registry still operative? If not, until what date was data collected? Is the data accessible?	PenTAG to contact lead author, Prof John Wagstaff
REMARCC (Registry for Metastatic RCC)	Does the registry only cover patients undergoing cytoreductive nephrectomy? Does it cover UK patients? Is the data accessible?	PenTAG to contact lead authors from recent REMARCC papers

RWE/observational studies search strategies

Database(s): **Ovid MEDLINE(R) ALL** 1946 to January 18, 2023
Search Strategy:

#	Searches	Results
1	exp renal cell carcinoma/	39106
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	79866
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	50806
4	or/1-3	86203
5	epidemiologic studies/	9242
6	exp case control studies/	1383274
7	exp cohort studies/	2436199
8	case control.tw.	149642
9	(cohort adj (study or studies)).tw.	298113
10	Cohort analy$.tw.	11161
11	(Follow up adj (study or studies)).tw.	55254
12	(observational adj (study or studies)).tw.	152540
13	Longitudinal.tw.	309912
14	Retrospective.tw.	710258
15	Cross sectional.tw.	487001
16	Cross-sectional studies/	453088

17	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	3683297
18	exp United Kingdom/	387773
19	(national health service* or nhs*).ti,ab,in.	259935
20	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.	47619
21	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.	2390072
22	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.	1693813

23	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.	67988
24	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.	249588
25	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.	32629
26	or/18-25	2999945
27	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp australia/ or exp oceania/) not (exp United Kingdom/ or europe/)	3275806
28	26 not 27	2841192
29	4 and 17 and 28	1251
30	limit 29 to yr="2020 -Current"	366

Database(s): **Embase** 1974 to 2023 January 18
Search Strategy:

#	Searches	Results
1	exp renal cell carcinoma/	31651
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	114735
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	77643
4	or/1-3	129418
5	clinical study/	161553
6	case control study/	197739
7	family study/	25736
8	longitudinal study/	184564
9	retrospective study/	1369707
10	prospective study/	823747
11	randomized controlled trials/	243369
12	10 not 11	813913
13	cohort analysis/	946930
14	(Cohort adj (study or studies)).mp.	440220
15	(Case control adj (study or studies)).tw.	161491
16	(follow up adj (study or studies)).tw.	71582
17	(observational adj (study or studies)).tw.	236491
18	(epidemiologic$ adj (study or studies)).tw.	119127
19	(cross sectional adj (study or studies)).tw.	316300

20	5 or 6 or 7 or 8 or 9 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	3690630
21	exp United Kingdom/	454479
22	(national health service* or nhs*).ti,ab,in.	382750
23	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.	56885
24	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.	3531748
25	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.	2792236

26	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.	114888
27	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.	384661
28	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.	53366
29	or/21-28	4321352
30	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp australia/ or exp oceania/) not (exp United Kingdom/ or europe/)	3508127
31	29 not 30	4073353
32	4 and 20 and 31	2210
33	limit 32 to yr="2020 -Current"	852